Sobering remedies

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SOBERING REMEDIES

A literature study regarding the efficacy and applicability of various substances to counteract the effects of ethanol consumption

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SUMMARY

The effects of ethanol can be counteracted essentially in three ways:
- By making the stomach empty more slowly. This retards the absorption of ethanol by the blood and the blood-ethanol concentrations are not as high. Consequently, the ethanol effect on the central nervous system will also be lessened.
All kinds of food, especially carbohydrates, prove effective in this respect.
- By directly influencing ethanol's effect without lowering blood-ethanol concentrations.
Levodopa and, to a still lesser degree, ephedrine and aminophylline, may have some direct influence on ethanol's central effects. The frequent side-effects, especially nausea and vomiting, however, make these unsuitable as sobering remedies.
- By promoting ethanol breakdown.
Large doses of fructose administered intravenously are effective in this respect. Fructose is not usable, however, because of the mode of administration, the large amounts needed, and the potentially dangerous biochemical modifications.

The best way of counteracting the influence of ethanol is to slow down absorption by means of a sugar-containing beverage or a substantial meal.
There seems little point at present in further research into sobering remedies as a means of promoting road safety.

ACKNOWLEDGEMENT

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CONTENTS

PREFACE

In March 1979 a SWOV report on "Drinking and Road Safety" was presented to the Road Safety Directorate of the Ministry of Transport and Public Works. It is being used for interdepartmental consultations on measures and activities aimed at limiting drinking and its dangers in road traffic. The report mentions research into sobering remedies as one of the future possibilities of lessening drinking hazards.

In order to take stock of present knowledge on this subject and to answer the question whether there is any point in encouraging further research into sobering remedies, a literature study was undertaken. This was carried out at SWOV's request by G. van den Brink and J.J. de Gier, both pharmacists in the sub-faculty of Pharmacy at Utrecht State University.

E. Asmussen
Director Institute for Road Safety Research SWOV

1. INTRODUCTION

Strictly speaking, a sobering remedy is a substance taken after drinking ethanol to eliminate its effects. In the present report, however, a sobering remedy is more widely defined. Substances used before or during ethanol consumption in order to obviate its effects will also be discussed. (The name alcohol commonly used for ethanol is really too wide. Alcohol is a general term for hydrocarbon compounds containing a hydroxyl group; ethanol is one of these compounds.)

Ethanol consumption may have favourable and unfavourable effects. Whether an effect is considered favourable or unfavourable will largely depend on the circumstances in which it occurs. Very little is known about the effects of ethanol that are responsible for traffic accidents. In this report, therefore, all effects will for the time being be regarded as unfavourable. Nevertheless, the different effects will be of varying importance to road safety.
This literature study will endeavour to answer the question whether remedies exist that can counteract the effects of ethanol and, if so, to what extent. It will then be considered whether there is any point in encouraging research into such remedies and, if so, what preparations the research should concentrate on.
In order to clarify to some extent the possible action of sobering remedies, this report will first explain the absorption of ethanol by the bloodstream, its distribution over the human body and its breakdown (under the common denominator pharmacokinetics), and also its effects on the central nervous system (psychopharmacology).

2.1. Absorption by the bloodstream

Three processes are of importance for the absorption of consumed ethanol by the bloodstream:
- absorption in the stomach: rapid but little;
- emptying of the stomach;
- absorption by the small intestine: rapid and complete, independently of food (Ritchie, 1975).

The principal step determining absorption of ethanol by the bloodstream is the emptying of the stomach. Transportation from the stomach to the duodenum takes place via the pylorus sphincter. The most fluid part of the stomach contents is transported first. At set times - usually once or twice a minute - the stomach passes part of its contents to the duodenum as the pylorus sphincter opens. This mechanism is known as the pylorus reflex.
Emptying of the stomach is influenced by the autonomous nervous system but is determined primarily by local factors such as volume and nature of stomach contents. Highly concentrated (hypertonic) solutions for instance retard the pylorus reflex. High concentrations of ethanol can cause cramp in the pylorus sphincter and thus delay transportation to the duodenum (the first portion of the small intestine). This retards absorption of ethanol by the bloodstream (Welling et al., 1977). Food can also retard the pylorus reflex. Ethanol in the stomach at the same time as food will therefore reach the duodenum later and more gradually. Consequently, less ethanol is absorbed by the bloodstream per unit of time (Sedman et al., 1976; Welling et al., 1977).

An attempt to approximate the absorption process to some extent can be made with simple models and formulas:
- Sedman et al. (1976) prefer first-order kinetics: the volume of ethanol absorbed per unit of time is proportionate to that available for absorption. Doubling the available volume doubles the volume absorbed per minute.
- Welling et al. (1977) determined a large number of blood-ethanol concentrations in six subjects. The results were defined best of all by the Michaëlis-Menten equation. Absorption according to this equation resembles first-order kinetics: the volume of ethanol absorbed per unit of time depends on the available volume but is not directly proportionate to it.

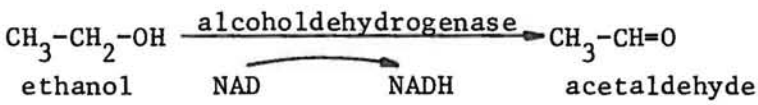
It is not possible to express a preference based on the available data either for the first-order model or for the Michaëlis-Menten equation.

2.2. Distribution in the body

After absorption by the bloodstream ethanol is rapidly transported through the body and dispersed in all the body fluids. Even in the brain, concentrations are quickly reached of the same magnitude as in the plasma (Ritchie, 1975).
The brain-ethanol concentration is determined by the arterial-blood concentration. If ethanol dispersion is not yet completed, capillary blood provides better information on the brain concentration than venous blood (Wagner et al., 1976). This is because the composition of capillary blood corresponds fairly closely to that of arterial blood.

2.3. Breakdown

Ethanol is broken down in the body mainly by the liver. Only about 2% is excreted otherwise, mainly via the urine and the breath. This may be as much as 10% with high blood-ethanol concentrations (Ritchie, 1975).
The liver oxidises ethanol to acetaldehyde by means of the ethanol dehydrogenase enzyme (an enzyme is protein catalysing a reaction or type of reaction). NAD (nicotinamide adenine dinucleotide) functions as a hydrogen acceptor in this reaction, i.e. a substance able to combine the hydrogen released by the reaction.



Thieden et al. (1972) say that it is not the amount of enzymes but the available NAD that determines the reaction velocity.
The acetaldehyde is next converted into acetyl co-enzyme A. The body can use this for various syntheses. This co-enzyme can also take part in the critic acid cycle, the net result of which is that energy is released in a form the cell can use. Acetyl co-enzyme A is broken down in this cycle into carbon dioxide and water (Ritchie, 1975; Bowman et al., 1970).
It is not material to the further discussion whether the amount of NAD or that of the enzymes determines the speed; in pharmacokinetics, however, it is customary to use enzyme occupation and so on.

The traditional view of ethanol breakdown is that it is a zero-order process: at the customary concentrations the oxidising enzymes are fully occupied and act at full speed. This means that a constant volume of ethanol is converted per unit of time regardless of the concentration in the blood.
Only at very low blood-ethanol concentrations (< 10 mg/100 ml) would breakdown depend on these concentrations. In this case, there is a first-order process and a constant percentage is eliminated per unit of time. The slope of the declining leg of

the ethanol curve is called β_{60}. This represents the hourly decrease in the number of mg ethanol per ml blood. In the literature, this averages 12 to 13 ml/100 ml (Kraemer et al., 1977; Besserer & Springer, 1971; Goldberg, 1974). For a male adult, this corresponds to the combustion of 7 grams of ethanol per hour (Goldberg, 1974).
There are constant references in the literature to the term AUC (area under the curve). This means the area in the concentration/time graph bounded by the concentration curve and the time axis. It is a measure of the volume administered becoming available to the body. Comparison of two curves - one obtained after oral administration and one after intravenous administration - permits an assessment of the volume absorbed from the gastro-enteric tract. This method is usable only with first-order kinetics, i.e. for ethanol concentrations < about 10 mg/100 ml blood. In practice, the concentrations are usually higher, and there is little point in using the first-order model, or the AUC.

Wagner et al. (1976) find that the breakdown rate of ethanol at concentrations of > 10 mg/100 ml does indeed depend on the concentration. They propose that the Michaëlis-Menten equation should be used to describe the blood-ethanol curve. Experimental concentrations in the blood after administration of various doses of ethanol conform excellently to this equation.
Definition of breakdown with the Michaëlis-Menten formula approximates the maximum enzyme occupation. Halving the ethanol concentration reduces the number of occupied enzymes, but this is not halved as would theoretically by the case with first-order kinetics. It is undoubtedly more correct to construct the blood-ethanol concentration curve with the Michaëlis-Menten equation than with zero-order kinetics. But this is a rather complex formula to use. The zero-order model is very simple for obtaining a quick idea of blood-ethanol curves.

3. PSYCHOPHARMACOLOGY OF ETHANOL

3.1. Effects on the central nervous system

The effects of ethanol on the central nervous system depend, inter alia, on the brain-ethanol concentration which in turn is correlated with the blood-ethanol concentration. Mental and physical effects are demonstrable at concentrations of < 50 mg/100 ml. Ethanol reduces the activity of the central nervous system. The most complex brain structures partly responsible for coordinating the various portions of the brain are influenced first, with the consequence of impaired judgement and confused thinking (Ritchie, 1975; Martindale, 1977). Especially at higher doses, there is a change of mood and of personality. Emotional outbursts are possible.

Non-psychical effects presumably also largely due to the action of ethanol on the central nervous system are: impaired coordination of movements, dilatation of the cutaneous blood vessels and stimulation of urine production. Coma can occur at an ethanol concentration of 300 mg/100 ml. Death due to extreme suppression of respiration is possible at 400 mg/100 ml blood (Martindale, 1977). Chronic consumption of large quantities of ethanol can cause liver damage; it is not clear to what extent a wrong diet or vitamin deficiencies play a part in this (Ritchie, 1975).

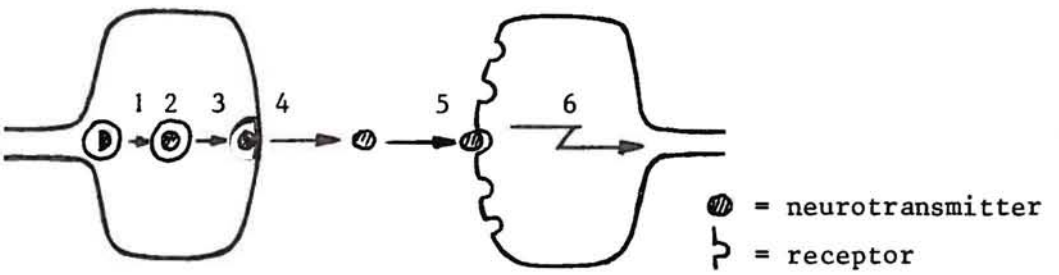
Shakespeare has already been quoted by various authors on the overall effects of ethanol: "..... and drink, sir, is a great provoker of three things .....: nose-painting, sleep and urine. Lechery, sir, it provokes and unprovokes: it provokes the desire, but it takes away the performance" (Macbeth Act II, Scene 3).

3.2. Sites of action

Research in recent years into the mechanism of action of ethanol in the central nervous system has concentrated increasingly upon its effects on the metabolism of neurotransmitters in the brain. Before anything is said about these effects, some information will be given on the role of neurotransmitters in conducting impulses. The conduction of an impulse across a nerve cell (neuron) is an electric process: after stimulation, an action potential occurs on the surface of a neuron membrane, causing a weak current to flow from outside into the inside of the cell through the membrane. Ethanol can suppress conduction of a stimulus in nerves because it directly affects generation and transmission of the action potential. However, this needs much higher concentrations than those already affecting the central nervous system (Ritchie, 1975). The stimulus is not transmitted from one neuron to another elec-

trically. Under the influence of the electric signal, substances are released at the end of a neuron which stimulate the next neuron to generate an action potential. These substances are called neurotransmitters. Important neurotransmitters are the catecholamines (especially noradrenaline and dopamine) and serotonin (= 5-hydroxytryptamine). These substances are not uniformly distributed throughout the brain: one substance plays a major role in some portions and another substance in others. How stimuli are transmitted by neurotransmitters can be seem from the following, very schematic illustration:

neuron terminal



1 = neurotransmitter synthesis
2 = neurotransmitter in granule
3 = granule moves to neuron surface
4 = neurotransmitter is released
5 = neurotransmitter occupies receptor
6 = electric signal is generated, ultimately resulting in a specific effect.

Ethanol stimulates both synthesis and breakdown of neurotransmitters. But both effects are not as strong for all neurotransmitters, and the concentration of one changes more than of the other. In mice under the influence of ethanol the dopamine/noradrenaline ratio is somewhat higher, while the total quantity of noradrenaline in the brain decreases slightly (Carlsson et al., 1973). Mice used in such experiments are usually given high doses of ethanol: 4 to 7 grams per kg body-weight, resulting in blood-ethanol concentrations of about 400 mg/100 ml. Such volumes lead to coma and are fatal for a number of laboratory animals (Penn, 1975). It cannot be judged whether effects observed in this way also occur with "normal" doses in human beings.
The action of ethanol is unlikely to be based on its conversion product acetaldehyde: the stimulating effect of ethanol on the production of catecholamines does not change if conversion into acetaldehyde is blocked (Svensson & Waldeck, 1973). Nor does acetaldehyde - in concentrations likely after ethanol breakdown - have any influence on the electroencephalogram (EEG) (Mikeska & Klemm, 1979).
The example of two medicines can be used to give some illustra-

tion of prevailing ideas on the influence of central catecholamines. Counteraction of the effects of dopamine in the limbic system with neuroleptics is attended by a lessening of psychotic symptoms in schizophrenic patients (the limbic system ensures, among other things, the translation of emotions into forms of physical expression). In depressive patients, an increase especially of the noradrenaline concentration with tricyclic antidepressants is accompanied by lessened depression. It is by no means certain that the changes in catecholamine concentrations brought about by these medicines are the direct cause of the psychological effects. Although the same applies to ethanol, the hypothesis can be stated that the action of catecholamines (especially dopamine) must be strengthened in order to counteract the psychic effects of ethanol.

In theory, the action of neurotransmitters can be augmented in various ways; three of these are:
a. Promotion of synthesis. Levodopa is converted into dopamine, one result being that the brain contains more of this neurotransmitter to occupy the receptors.
Alkana et al. (1977) claim that levodopa counteracts the central effects of ethanol.
b. Promotion of the processes causing the signal. Aminophylline retards the breakdown of a substance (cyclic AMP) needed to cause the effect of catecholamines. Alkana et al. (1977) believe that the central effects of ethanol are reduced by administering aminophylline.
c. Promotion of the effects of another stimulating system. Stimulants such as caffeine and amphetamine are said to counteract the soporific effects and performance impairment caused by ethanol.

Theoretically, the effect of neurotransmitters can be counteracted as follows:
a. Retarding the synthesis (stage 1 in the diagram). Alpha-methylthyrosine is a substance that retards the synthesis of dopamine and noradrenaline. It can counteract the mobility and euphoric action of ethanol in both mice and human beings (Strömbom et al., 1977). These effects of ethanol are unlikely to be the result of a direct stimulant action but are caused by suppression of brain systems with an inhibiting function which are the most susceptible to ethanol (Ritchie, 1975).
Alpha-methylthyrosine, similarly to ethanol in slightly higher concentrations, retards not only catecholamine synthesis in the inhibiting systems but also synthesis in the stimulating systems. The net effect is thus suppression of brain activity.
b. Retarding release (stage 4 in the diagram). Clonidine and apomorphine are said to reduce the amount of noradrenaline and dopamine released.
Similarly to alpha-methylthyrosine these two medicines also

counteract increased mobility in mice after low doses of ethanol (Carlsson et al., 1973).
c. Counteracting the effect at receptor level (stage 5 in the diagram). Propranolol is a substance which occupies the receptors, like the neurotransmitters. In contrast to occupation by the neurotransmitters, that by propranolol causes no signal however; stage 6 is not reached, therefore.
The dulling of the central nervous system by ethanol is said to be intensified somewhat by propranolol (Alkana et al., 1977).

It is simpler to intensify the disturbance of an equilibrium than to (partly) restore it. Dopamine, noradrenaline and serotonin all probably have different functions in causing the symptoms of ethanol consumption. A remedy to counteract the central effects of ethanol must at least be able to neutralise the activity of these three neurotransmitters again; this disregards other possible sites of ethanol action. In view of the delicate balance and the close interrelationship of the three neurotransmitter systems it will be clear that such a remedy is not easy to find. A combination of remedies would thus seem more appropriate.

4. RESEARCH INTO THE EFFECTS OF SOBERING REMEDIES

4.1. Research method

Evaluation of research results necessitates some knowledge of the ways in which research can be planned and the limitations of the various methods.

The most obvious way to assess the effect of a substance believed to change blood-ethanol concentrations and/or performance after ethanol consumption is to compare two groups of subjects. Both groups are given the same volume of ethanol to drink; one group takes the substance being tested and the other (the controls) does not. A refinement is the cross-over test: each subject is assessed in two situations, once with and once without the remedy, so that each subject acts as his own control.

It is often incorrect merely to refrain from giving the remedy to the control group, as an example will illustrate: Luff et al. (1970) made cross-over tests of the effect of 400 to 500 ml of "Sangrita" on blood-ethanol concentrations. Each subject was given, in addition to ethanol, Sangrita one time and nothing the other. A substantial reduction in blood-ethanol concentrations was noted by drinking Sangrita. But if the Sangrita drinkers had drunk half a litre of water instead of Sangrita this would also have produced lower ethanol concentrations owing to a diluting effect. The investigators are not, of course, interested in this aspecific dilution action but in any specific action reducing blood-ethanol concentration. To assess this specific action the control group should be given an equal volume of water or Sangrita base without the constituent regarded as active (as a placebo). This was indeed done in later research (Luff & Raudonat, 1972). The action of Sangrita now proved to be much less spectacular (see further Section 5.1.).

In open tests both the investigator and the subject know when the tested remedy is being taken and when it is not. Such tests are useful only for factors that cannot be psychologically influenced. Asking subjects who know whether or not they have taken a "sobering remedy" about their degree of intoxication is therefore purposeless for evaluating its effect (Besserer & Springer, 1971).

A single blind test is one in which the investigator knows who is given what while the subject does not. Although this method is much more reliable for evaluating subjective magnitudes than open tests, there is always a danger of the investigator's expectations influencing the results.

A double blind test is the most reliable. Neither the investigator nor the subject knows whether the tested remedy or a placebo (or some other reference) has been administered.

In blind tests (single or double) there must be no possibility

whatever of distinguishing between the remedy and the placebo. Noble (1974) notes this in connection with a very characteristic problem: the "Sted-eze" he was to test contains yeast and other B vitamins readily detected from their smell. The "blindness" should be checked in every test. Auty & Branch (1977) do this in fact: the three ethanol-containing drinks they used could not be distinguished from one another by the subjects.

4.2. Measuring the effects of ethanol

Various tests are possible for measuring the effects of ethanol on human functions. Most test programmes measure in some way its influence upon the ability to concentrate and the memory. Others measure especially movement coordination or deal specifically with the influence on the disposition.
Of all processes influenced by ethanol, central information assimilation is most susceptible (OECD, 1978). It is not clear in many testing methods what relevance the results have for routine functioning and especially driving skills.

4.2.1. Concentration

The Bourdon letter-checking test is sensitive to ethanol effects, according to Osterhaus (1973): the subject has to tick certain letters from among a much bigger presentation, the number of errors and the speed being recorded. The most common concentration test in The Netherlands is a variant of this: the Bourdon-Wiersma test. Four-dot figures have to be ticked in a field containing three, four and five-dot figures (Sijbrant-Schreuder & Sijbrant, 1979). Arithmetical and counting tests are suitable for measuring the degree to which ethanol influences thinking and concentration, for example simple additions and substractions or counting back from a thousand (Osterhaus, 1973). The latter test is also claimed to measure endurance (Sijbrant-Schreuder & Sijbrant, 1979).

4.2.2. Memory

The memory is affected by ethanol. Noble (1974) gets his subjects to listen to a series of words which they have to repeat as fully as possible.

4.2.3. The mind

Osterhaus (1973) attaches great value to handwriting comparison. Personality changes are claimed to be demonstrable by this means even at low concentrations. Luff et al. (1970) use the tree test for this: the subjects are asked to draw a tree; an expert can derive personality data from the tree's appearance.
Influence of the disposition can be measured well by asking the subject to complete a scoring list himself (Sijbrant-Schreuder & Sijbrant, 1979).

4.2.4. Information assimilation

Various projects (Alkana et al., 1976 and 1977; Noble, 1974) present in a test procedure both a tone and a series of numbers. When the tone is heard the person must respond by giving a signal; the numbers must be repeated. This test may also be useful for measuring the mental load. The authors say this measures the accuracy with which the information is assimilated.
Performance is significantly affected even at low ethanol concentrations in tests during which various tasks have to be performed simultaneously (Müller-Limmroth, 1968).

4.2.5. Coordination and response rate

Alkana et al. (1976 and 1977) and Noble (1974) use a platform-balancing test for measuring disturbances in equilibrium due to ethanol. The results of this method are rather erratic; the authors themselves (Noble, 1974) are not clear about the significance of a positive score with this procedure.
A sounder method of measuring muscle coordination would seem to be to measure the steadiness of the subject's hand: he has to hold a bar in a small opening; the number of times the bar touches the sides and the contact time are measured (Luff et al., 1970).
Response time is also influenced by ethanol. Mallach et al. (1977) say that measuring the response rate to an optical stimulus is a sensitive testing method.

4.2.6. Electroencephalogram (EEG)

Ethanol slows down all kinds of EEG wave frequencies. This is usually associated with reduced alertness or sleep (Noble, 1974).

4.3. The role of the blood-ethanol concentration

Pharmacokinetics investigates blood-ethanol concentration curves in terms of time related to many variables such as volume and rate of drinking. Psychopharmacological knowledge makes it clear that the blood-ethanol concentration is important in clarifying effects. It is usually investigated, therefore, what effects are found in relation to the blood-ethanol concentration. On the basis of various investigations, the blood-ethanol concentration can even be used as a measure of an individual's intoxication.
Investigation of substances influencing the central effects of ethanol, however, relates in fact to the extent to which the relationship between blood-ethanol concentration and the effects is disturbed.
There are indications that an important aspect of the relationship between blood-ethanol concentration and the effects is whether the concentration rises or falls and how quickly. Ritchie (1975) reports that the effects of a given blood-ethanol concentration are greater when the concentration is rising than when it is falling. Osterhaus (1973) speaks of a stronger effect the quicker the concentration rises. In research by Goldberg (1974) maximum subjective intoxication is reached before the blood-ethanol concentration is at its maximum.

The blood-ethanol concentration can be determined not only from a blood sample but also from a breath sample: the breath-ethanol concentration bears a fixed ratio to the blood-ethanol concentration. It is less inconvenient for a subject to give a breath sample than a blood sample.
It is also possible to determine the ethanol concentration in the saliva; the figures so obtained practically agree with the blood-ethanol concentrations (Friedemann et al., 1938).

5. INFLUENCING ETHANOL PHARMACOKINETICS AND PSYCHOPHARMACOLOGY BY VARIOUS SUBSTANCES

5.1. Influencing the absorption of ethanol by the bloodstream

- By food

Sedman et al. (1976) investigated the influence of various kinds of food on blood-ethanol concentrations. Ten minutes before drinking a beverage containing a quantity of ethanol (45 ml 95%-ethanol + 105 ml orange juice) the subject was given one of the following "meals":
- 200 ml water;
- 200 ml single cream (= fat);
- 20 g "Somagen" in 200 ml water (= protein);
- 80 g glucose in 200 ml water (= carbohydrate).

Half an hour after drinking water following by the ethanol-containing drink, a maximum blood-ethanol concentration of 69 mg/100 ml was reached. About an hour after taking fat or protein a maximum concentration of 50 mg/100 ml was measured. After the carbohydrate meal the maximum concentration was only 36 mg/100 ml; this was reached after 1½ to 2 hours.
200 ml of sugar solution with a glucose content of 40% w/v is thus able almost to halve the maximum blood-ethanol concentration if drunk shortly before the ethanol. This effect can be explained from the observations of Eisner & Berger (1971): drinking 100 grams of glucose in 750 ml water causes the stomach to empty six times slower than drinking 750 ml water alone. Computer simulations by Sedman et al. (1976) give the impression in the first instance that ethanol absorption is incomplete, but prove to agree with complete absorption according to the first-order model.

Welling et al. (1977) also examined the influence of carbohydrate, fat and protein meals on blood-ethanol concentrations. Immediately after a meal a small quantity of ethanol (0.16 g per kg body-weight) was given in 150 ml water. The control group was not given a meal: only the ethanol drink. Half an hour after drinking the ethanol the control group reached a maximum blood-ethanol concentration of 16 mg/100 ml. In this research, too, carbohydrate was found to have the greatest influence on blood-ethanol concentration (maximum 1 mg/100 ml), followed by fat (maximum 2 mg/100 ml) and protein (maximum 7 mg/100 ml).
In the context of a report on sobering remedies, Welling et al.'s data are less relevant. With the volume of ethanol consumed, roughly equivalent to one good glass, there is little point in lowering the blood-ethanol concentration.
Yoghurt and a large amount of milk (850 ml) can also slow down ethanol absorption (Martindale, 1977).

Conclusions
The widely known maxim that one gets less easily intoxicated after drinking on a full stomach is confirmed by research. Carbohydrates, and other foods too, delay the absorption of ethanol drunk shortly after.

- By Alsaver
Alsaver syrup is a beverage consisting of 71% sugar, largely glucose and fructose. There is also a dry powder form on the market (Goldberg, 1974).

Spann et al. (1977) compared the effect of 200 ml Alsaver on blood-ethanol concentrations with that of 200 ml sugarless placebo (low-carbonate mineral water with a colouring). The ethanol was drunk in the form of whisky within three quarters of an hour of drinking the Alsaver or placebo. The maximum blood-ethanol concentrations in the Alsaver group were 4 mg to 12 mg/100 ml lower than in the placebo group (70 too 100 mg/100 ml).
The tendency is clear but none of the differences was statistically significant. Under the influence of Alsaver the maximum blood-ethanol concentrations were also reached later. The authors explain the action of Alsaver as a delaying effect on ethanol absorption.

Although Alsaver's sugar content is much higher than that of the sugar solution Sedman et al. (1976) administered, the latter found a greater retarding effect on absorption of ethanol by the blood-stream. The explanation must lie in the fact that Spann et al. gave their subjects a meal half an hour before drinking began. Sedman et al.'s subjects had nothing to eat during the ten hours preceding the tests. A meal itself slows down ethanol absorption, making it more difficult to trace the difference in effect between an "absorption retarder" and a placebo taken afterwards.

Goldberg (1974) also investigated the effect of Alsaver syrup and powder. His subjects were given 0.7 grams ethanol per kg body-weight, together with 2.7 ml Alsaver syrup per gram ethanol. The Alsaver syrup was diluted with water in the ratio 3 : 10.
The reference was non-sugar Alsaver solvent (water?).
The selected procedure was rather remarkable in that the quantity of food eaten before commencement of the experiment was varied.
Under the influence of Alsaver, the maximum blood-ethanol concentration was reached a little later, while the peak was lower (55 mg as against 78 mg/100 ml). It is not stated whether this difference was statistically significant.

Conclusions
Alsaver, taken at the same time as ethanol, probably results in a reduction of the maximum blood-ethanol concentrations. This effect is presumably due to this sugar-containing drink delaying emptying of the stomach, and hence ethanol absorption.

- By Mobiletten

The quantitative composition of this preparation is not known. The manufacturer states it consists of beet-sugar products, protein and fructose.

Kraemer et al. (1977) examined the effect of Mobiletten on blood-ethanol concentrations. Within the space of ten minutes the subjects drank 0.75 gram of ethanol per kg body-weight in the form of vodka. Five minutes before and immediately after drinking, 20 grams of Mobiletten was taken mixed with 150 ml mineral water. The control group were given no Mobiletten, but did have vodka and mineral water. All the subjects had an identical lunch 1½ hours before the test commenced.
Under the influence of Mobiletten, the maximum ethanol concentrations were reached later (two hours instead of 1½ hours later). The maxima were also lower (43 mg instead of 63 mg/100 ml). This difference is statistically significant.
Mobiletten presumably consists largely of carbohydrates. The lower maximum blood-ethanol concentrations will thus probably be caused by a retarding effect of carbohydrates on the emptying of the stomach.

Conclusions

Mobiletten can lower the maximum blood-ethanol concentration if taken at about the same time as the ethanolic drink.

- By Almi (Alkohol Minus)

This drink proves to consist of 20% honey, 1.8 grams acetic acid per litre and 3.1 grams of other acids per litre (Rauschke, 1968).

Rauschke compared blood-ethanol concentrations in three situations: after Almi, after a mixture of honey, lemon and water, and after orange juice. All three drinks were given in doses of 2 x 0.33 litre (0.66 litre of Almi contains 115 grams of sugar).
Since three different drinks were tested with the modest number of fourteen subjects, moreover including a subdivision into use before and during ethanol consumption, no valid conclusions can really be drawn from the test results.

Conclusions

It cannot be inferred from Rauschke's experiments whether Almi not only has a diluting effect but also a specific delaying action on ethanol absorption. This is likely, however, having regard to the high sugar content.

- By Sangrita

Sangrita is a Mexican spiced drink containing, among other things, the following ingredients: vinegar, Spanish pepper, black pepper, ginger, garlic, coriander, nutmeg, dille, mustard and cinnamon. The base appears to be a kind of tomato juice (Luff et al., 1970; Luff & Raudonat, 1972).

Luff et al. (1970) examined the effect of 400 to 500 ml Sangrita Picante, the spicier of the two products on the market. Ethanol (0.95 gram per kg body-weight) was given in the form of brandy. In the Sangrita group, the maximum blood-ethanol concentrations were significantly lower. The control group were given brandy only.
Any effect of Sangrita, apart from specific dilution and consequent slower absorption, is not demonstrated with this test.

Luff & Raudonat (1972) did try to demonstrate a specific effect of Sangrita. It was compared not only with "no remedy", but also with the same volume of tomato juice. The diluting effect observable from the lower ethanol concentration curve after drinking tomato juice is evident. In addition, Sangrita seems to cause an additional reduction. It is not stated whether this difference is statistically significant.

Osterhaus (1973) found slower ethanol absorption after drinking 150-200 ml of Sangrita. Here, too, the control group were not given a placebo.

Conclusions
It is possible that the spiced drink Sangrita lowers the blood-ethanol concentration if taken simultaneously with the ethanolic beverage. More data are needed, however, for a reliable opinion.

5.2. Influencing ethanol effects on the central nervous system

- By Mobiletten
Kraemer et al. (1977) and Mallach et al. (1977) made cross-over tests covering 15 subjects on the effect of Mobiletten on blood-ethanol concentrations and a number of psychological and physical factors. A quarter of an hour after commencement of the drinking time, i.e. five minutes after the end of this, better results were obtained in three tests with the Mobiletten group (measurement of response rate to optical stimuli; duration of a test in which 20 contacts on a plate had to be touched with a pen held in the left hand; duration of the same test but using both hands). One hour and two hours after commencement of the drinking period in the Mobiletten group, only the response rate to an optical stimulus was better than in the non-Mobiletten group.
It is striking that with the same blood-ethanol concentrations, their effects in the Mobiletten group were less than in the non-Mobiletten group (Mallach et al., 1977). This suggests that the effect of ethanol depends not only on the absolute concentration in the blood but also on the absorption rate.
Research by Kraemer et al. (1977) shows that Mobiletten delays ethanol absorption.

- By Alsaver

Goldberg (1974) made cross-over tests with four subjects on the influence of Alsaver on blood-ethanol concentrations, firmness of grip and subjective intoxication. The effect on performance roughly corresponded to the blood-ethanol concentration.
There is no indication of any inherent effect by Alsaver on central ethanol effects, i.e. apart from delayed absorption.

- By Sangrita

Luff et al. (1970) and Luff & Raudonat (1972) found that ethanol worsened simulated-driving behaviour and lengthened response time. Remarkably enough, the combination of ethanol and Sangrita led to better performance compared with a control rating recorded before ethanol consumption.
It cannot reasonably be assumed, however, that there is any genuine improvement: the control ratings were not determined under the same conditions as the ethanol/Sangrita ratings. The better performance was probably due to a learning process.
Yet it can be concluded that simulated-driving behaviour after drinking ethanol plus Sangrita is better than after drinking ethanol alone. This is explained by differences in blood-ethanol concentrations between the two groups.

Subjective intoxication after drinking ethanol plus Sangrita was distinctly lower than after ethanol alone. The fact that the subjects knew when they were given the drink under test (open testing) and that they were probably aware of the expected effects greatly reduced the value of the differences: the subjects' pattern of expectations is bound to have influenced their judgment of the degree of intoxication.

Osterhaus (1973) considers the Bourdon letter-checking test suitable for (objective) measurement of intoxication. It produced no demonstrable difference between drinking Sangrita or not in the case of twenty subjects all of whom had been given an unstated amount of ethanol to drink and nine of whom also had the Sangrita spiced drink. In the Sangrita group the blood-ethanol concentrations were considerably lower however.

- By Sobaro

Sobaro is advertised as a sobering remedy. One Sobaro capsule contains 500 mg charcoal, 100 mg kaolin (hydrated aluminium silicate) and 100 mg ascorbic acid (vitamin C). Vitamin C is said to promote ethanol breakdown, while the other two ingredients are claimed to absorb the "Alkoholdämpfe" (alcohol fumes). The dose is 1 capsule per unit of drink (a quarter litre of wine or half a litre of beer).

The lower subjective intoxication under the influence of Sobaro found by Besserer & Springer (1971) is unrelated to blood-ethanol concentrations. Measurement of subjective intoxication is hardly of any value in such open tests.

- By Sted-eze

Sted-eze is a preparation consisting of a number of B vitamins. It has no effect on the symptoms caused by ethanol (Noble, 1974).

- By levodopa

Levodopa is a drug used to treat Parkinson's disease. Its action is based on the formation of dopamine from levodopa in the brain.

Alkana et al. (1977) gave 14 subjects 0.8 gram of ethanol per kg body-weight, in the form of gin and peppermint spread evenly over half an hour. A quarter of an hour after the end of the drinking time either 1.5 grams levodopa (Dopar®) or placebo was swallowed. This was a cross-over, double blind experiment.
A number of tests were next made, including platform-balancing test, divided-attention test and EEG.
In the platform-balancing test the subjects had to try and stay in balance for 20 seconds with their eyes closed on an unstable platform. Body adjustments were electronically recorded. Half an hour after levodopa had been taken it had caused a significantly improved performance compared with placebo treatment. But after 105 minutes the position was reversed, though this result had only low significance ($P < 0.10$). Noble (1974) states that the relevance of a positive result with this procedure is not clear.
In the divided-attention test the subject had to detect with one ear a tone against a background of noise; with the other ear he heard sets of six numbers he had to repeat. The levodopa group had fewer errors in tone perception. The authors' conclusion is that levodopa has a favourable effect on disturbed information assimilation after ethanol consumption.
The EEG for the levodopa group differed clearly from that in the placebo group: in the former, slow activity was reduced and rapid activity increased. This would imply that dulling of the central nervous system by ethanol is counteracted by levodopa.
In these tests levodopa had no influence on disposition, memory or degree of intoxication as stated by the subject himself and by an observer.

Alkana et al. (1977) use the same data as Noble (1974). There are some numerical differences that cause some doubt as to the accuracy of processing the results.

To sum up, it can be stated that no difference was found between levodopa and placebo in most behaviour tests. What differences were found (platform-balancing and divided-attention tests) may have been due to the lower blood-ethanol concentrations, as levodopa can slightly reduce blood-ethanol concentrations (by delaying the emptying of the stomach?): about 10 mg/100 ml with concentrations around 70 mg/100 ml. Some other active mechanism of levodopa, particularly a site of action in the brain, cannot however be precluded.

- By ephedrine

Ephedrine is a substance with a noradrenaline-like effect. It is used in bronchial asthma, but has largely fallen into disuse as new remedies with fewer side-effects have become available.

Alkana et al. (1977) and Noble (1974) compared for eight subjects in a number of test procedures (see levodopa) the effect of 50 mg ephedrine sulphate and placebo after taking 0.8 grams of ethanol per kg body-weight.
Half an hour later results with the platform-balancing test were better in the ephedrine group than in the placebo group.
Appraisal of disposition showed no pronounced differences. Objective intoxication noted by an observer seemed somewhat lower in the ephedrine group: fewer problems with walking were noted.
No influence was noted of ephedrine on memory or in the devided-attention test after ethanol consumption.
If ephedrine has any sobering action, it is only slight.

- By aminophylline

Aminophylline has an action corresponding to that of the catecholamines. It is used for various forms of difficulty in breathing.

In experiments by Alkana et al. (1977) and Noble (1974) eight subjects were given, in addition to ethanol, 200 mg aminophylline or placebo. Performance in the platform-balancing test was significantly improved by the influence of aminophylline, particularly 105 minutes after taking. The subjects in the aminophylline group were rated less dizzy. No effect was found on the other measured factors.
The same applied as to ephedrine: perhaps it has some effect.

- By the combination of ephedrine and aminophylline

This combination proves to have no effect whatsoever if the positive score after half an hour in the erratic platform-balancing test is disregarded (Alkana et al., 1977; Noble, 1974).

- By propranolol

Propranolol is a substance that counteracts the action of catecholamines.

Alkana et al. (1976) state that it is useless as a sobering remedy. Their test results agree with the assumption that the activity of the central catecholamines must be increased in order to counteract the central effects of ethanol.
If propranolol does have any effect on ethanol induced symptoms it is to augment them.

- By caffeine

Caffeine is a constituent of coffee, tea and cola, for instance. It is widely used in practice to counteract the influence of ethanol.

Animal experiments have demonstrated, however, that caffeine cannot be a good sobering remedy: the adverse effects of ethanol on making a correct choice and the time this takes is augmented by high doses of caffeine (Müller-Limroth, 1968). Little effect is likely from a few cups; adverse rather than favourable effects are experienced with a lot of coffee.

- By amphetamine

Amphetamine and its derivates can temporarily (!) suppress symptoms of fatigue. But judgment is impaired, and it is dangerous to use them in traffic. There is a genuine risk of addiction. No favourable action on the effects of ethanol was demonstrable. A number of unpredictable interactions were observed, however, in various test procedures (Soehring & Wolters, 1968).
The use of such substances as sobering remedies is perilous.

- By various other substances

A number of remedies were tested with animals only and were found to have a favourable effect on various ethanol-influenced factors.

Penn (1975) investigated the effect of the combination 5-hydroxymethylcytosine and pyridoxal. The former is a pyrimidine derivative whose structure resembles those in nucleic acids; pyridoxal belongs to the group of B6 vitamins.
In the case of mice whose peritoneum was injected with a high dose of ethanol (approx. 5 grams per kg body-weight), sleeping time was distinctly shortened if the combination of the two substances was administered in the same way. The combination had no effect on the blood-ethanol concentration.
The author states these substances can also be administered orally. It cannot be judged whether this research into the sleeping time of mice had any value for research into sobering remedies.

Prasad et al. (1977) examined the effect of histidylproline on the sleeping time of mice. This substance is a breakdown product of thyrotropine releasing hormone (TRH), i.e. the hypothalamus hormone inducing the hypophysis to release thyrotropine which in turn induces the thyroid gland to release thyroid hormones.
In mice administered with ethanol, sleeping time can be shortened by injecting the brain with histidylproline.
The need to inject it in the brain makes this substance unsuitable as a sobering remedy for human beings.

Injection in the peritoneum of a substance coded DL-524 likewise shortens the sleeping time of mice given ethanol (Griffis & Forney, 1977). The structure formula of DL-524 bears some resemblance to that of substances with a noradrenaline-like action.

Conclusions

As the action of ethanol depends on its concentration in the blood,

substances that can lower this may logically also lessen the central effects of ethanol. Only when a substance leads to improved performance with an unchanged blood-ethanol concentration, it is possible to speak of a central action. Most substances discussed in this section did not satisfy this condition in tests on subjects. Statements on possibly favourable results with levodopa, ephedrine and aminophylline are based on only one project, because Alkana et al. (1977) and Noble (1974) used the same data. This calls for some caution in drawing conclusions.

5.3. Influencing ethanol breakdown

- By fructose

Brown et al. (1972) investigated the effect on 19 patients with ethanolic poisoning of 500 ml of 40%-fructose solution compared with 500 ml of 0.9%-sodium chloride solution. Both solutions were administered as intravenous infusions.
The fructose group were able to eliminate the ethanol significantly quicker than the sodium chloride group (β_{60}: 27.6 mg as against 22.5 mg/100 ml an hour). The authors point out that the effects of fructose are erratic and therefore unpredictable for individual patients.

Levy (1977) compared for two groups of ten patients with acute ethanol poisoning, in a double blind test, the effect of 1000 ml of 10%-fructose solution with that of 1000 ml of 10%-glucose solution. (Glucose has never been found to have the effect of lowering blood-ethanol concentrations). Both solutions were administered intravenously. At the moment of administering the sugar the average blood-ethanol concentration was 340 mg/100 ml. There was no significant difference between the two groups in the reduction of the blood-ethanol concentration or in the patient's clinical picture. The authors conclude that the use of fructose for ethanol poisoning is unjustified because it has no greater effect than glucose.

The fact that Brown et al. did see some results from fructose therapy while Levy did not may be because Brown et al. administered 200 grams of fructose and Levy only 100 grams. However, even intravenous doses under 100 grams did have the effect of lowering blood-ethanol concentrations (Martindale, 1977).

The action of fructose is said to be based on the formation of NAD, a substance needed to convert ethanol into acetaldehyde (Thieden et al., 1972).

- By Sobaro

The effect of this preparation, whose composition is described in 5.2., on blood-ethanol concentrations was investigated by Besserer & Springer (1971). Sobaro had no effect whatsoever on the blood-ethanol concentration curve.

- By various other substances

It is striking how many remedies have appeared on the German market. Until recently, registration policy for pharmaceutical preparations in the Federal Republic was more flexible than in The Netherlands: the Dutch Council for the evaluation of drugs requires, inter alia, that the effectiveness of a preparation must have been demonstrated before it may be marketed.

Some authors (Rauschke, 1968; Besserer & Springer, 1971; Spann et. al., 1977) give an historical review of products marketed in Germany as sobering remedies in the course of the years. They also refer to the literature exposing these preparations as ineffective. They name: Pekasin, Gothania-antialkoholpastillen, Elektrovid, Polysan, Laevosan, Contra, Stop, Promill-Ex, Activit, Choco aus Milch, Bacchantyn and Bavarin 604.

Conclusions

Of the substances discussed in this section, only fructose administered intravenously in high doses can probably accelerate ethanol breakdown to some extent.

5.4. Summary

A number of substances slow down absorption of ethanol by the blood if they are taken shortly before or together with the ethanolic drink. The result is that the blood-ethanol concentration changes more slowly and does not reach as high a value. This counteracts a decreased performance after drinking.
First of all, various foods are suitable for delaying absorption: carbohydrates, fats and proteins. Carbohydrates in a dosage of 50 to 100 grams are most effective in retarding ethanol absorption.
A number of sugar-based preparations (Alsaver, Mobiletten and Almi) are also active.
Stimulants (for instance the spiced drink Sangrita) may also have a retarding effect.
Lastly, the blood-ethanol concentration is lowered somewhat by the drug levodopa (1.5 grams).

It is not impossible that levodopa, and to a lesser extent ephedrine and aminophylline, counteract the central effects of ethanol by direct action on the brain. But opinions on these substances are based on a single research project.
High doses (100 grams or more) of intravenously administered fructose can probably speed up ethanol breakdown to some extent.

- Alsaver, Mobiletten, Almi (and other sugar preparations)
It has been adequately demonstrated that at least several tens of grams of sugar taken at about the same time as ethanolic beverages reduce the action of ethanol. Especially when the sugar is taken on an empty stomach, the effect is also relevant for practical purposes.
Limitations and drawbacks of their use are:
a. the sugar-containing drink should be taken not more than about one hour before, or during, drinking; administration afterwards is pointless;
b. taking the sugary drink on a full stomach has little effect;
c. the volumes needed for results are fairly large; usually several hundred millilitres of the sugary drink will have to be taken;
d. taste may form a problem: Almi has an unpleasant taste (Rauschke, 1968); the honey drink examined by Rauschke also detracts from the flavour of the ethanolic drink.

Drinks with at least 50 grams of sugar per dose can be used as sobering remedies provided the above limitations are observed and the drawbacks are accepted. Such remedies can be of value in cases where people know in advance that they are going to drink and want to reduce the consequences to a minimum, for instance at receptions. The effect is then about the same as the traditional sobering remedy: the savoury cocktail meatball.

- Sangrita
As already stated, the effect of the spiced drink Sangrita requires further confirmation.
The large quantities needed (400 to 500 ml) are no drawback according to Luff et al. (1970) and Luff & Raudonat (1972); the drink is said to have a pleasant taste.

- Levodopa
The action of levodopa on ethanol-related effects requires further investigation.
Levodopa's applicability is limited by the risks attaching to use of this strong acting drug. The most common side-effects are nausea and vomiting; they also include constipation, lower blood pressure, muscular spasms, drowsiness, excitability, confusion and hallucinations (Lammers et al., 1975; Informatorium Medicamentorum, 1975). Three out of fourteen subjects (Alkana et al., 1977) did not complete the tests because of nausea; this also affected other subjects in these tests. As a comparison: treatment of Parkinson's disease starts with 0.25 grams a day, spread over three to four doses;

Alkana et al.'s subjects were given 1.5 grams of levodopa all at once. There are in fact two levodopa preparations on the market that cause fewer side-effects than the Dopar® that was used, i.e. Sinemet® and Madopar®. These, like remedies containing levodopa, are obtainable in The Netherlands on prescription only.

The use of levodopa as a sobering remedy is dissuaded: any slight result that may be achieved does not outweigh its potentially harmful side-effects.

-Ephedrine and aminophylline

About the same applies to these two substances as to levodopa: their effect has been inadequately researched; any action is probably slight and they are far from safe.
Known side-effects of ephedrine include: palpitations of the heart, restlessness, insomnia, dizziness and nausea. The use of aminophylline has caused, among other things, disturbances of the heart rhytm and nausea; overdoses are liable to cause headaches, dizziness and spasm (Informatorium Medicamentorum, 1975).
These two remedies will be tolerated better than levodopa, but on the other hand their effects are probably slighter. In The Netherlands tablets of 50 mg ephedrine and theophylline tablets (theophylline is the active ingredient in aminophylline) can be obtained from dispensaries without a prescription. But on the whole these will hardly be inclined to sell them for the dubious purpose of "sobering up".

The use of these as sobering remedies is dissuaded in view of their at most minor effect and the risk of complications.

- Fructose

This substance can accelerate ethanol breakdown. The possibility of using it as a sobering remedy is limited by a number of factors:
a. reasonably reliable action requires quantities over 100 grams;
b. taking large quantities of fructose may cause stomach ache and diarrhoea (Brown et al., 1972; Martindale, 1977);
c. fructose may have the effect of increasing the lactic acid and uric acid concentration (Levy, 1977); a high lactic acid concentration may turn the blood too acid, one possible consequence of which is loss of consciousness; an increased uric acid concentration can cause an attack of gout;
d. the best result is obtained after intravenous administration; fructose swallowed and reaching the stomach retards (like all sugars) the emptying of the stomach and its own absorption;
e. its effect on individual patients is difficult to predict.

In view of these factors it has to be concluded that fructose cannot be used in normal circumstances as a means of accelerating ethanol breakdown.

7. THE VALUE OF FURTHER RESEARCH

Sufficient knowledge exists about the retarding effect on ethanol absorption of sugars and a number of other substances. No definite opinion can be expressed about Sangrita without further research.

Further research is also needed in order to express a definite opinion on the effect of levodopa, aminophylline and ephedrine on the central action of ethanol. Having regard to the possible harmful side-effects of these drugs, however, there is little point in research regarding their use as sobering remedies. But further research into the interaction between levodopa and ethanol might give greater insight into the way ethanol affects the brain. Research in this direction, however, will primarily have a scientific purpose.
Going by information at present available it is unlikely that a remedy can be developed within the next few years which can satisfactorily counteract the various disturbances that ethanol causes in the highly complex central nervous system.

As regards the value of further research into substances promoting the breakdown of ethanol, it can be said that there are no indications that, apart from fructose, there are any remedies now, or remedies that could be developed in the near future which are effective on this point. The use of fructose should be confined to treating severe ethanol poisoning in specialised centres, for the reasons gone into extensively in the previous section.

In deciding the value of further research, attention should also be devoted to the psychological and social consequences of sobering remedies.

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