There is a need to antagonize the effects of ethanol (EtOH) in many clinical situations. Although the most intoxications with EtOH are not life-threatening, the figures for EtOH mortality are still high at least in Finland. An effective injectable antagonist would prove valuable when treating deeply comatous patients. If the patient concerned is not in actual coma but is conscious, he is often restless and aggressive and may need some sedation. The opinions vary as to what is the best suitable drug for the sedation of aggressive drunken individuals. Benzodiazepines and clomethiazole have been commonly used; unfortunately this practice has often resulted in death. As to clomethiazole in particular, its bioavailability is subject to great variations owing to a high first-pass extraction which in turn is altered in liver diseases (Blaschke & Rubin 1979). In animal studies conducted to find out eventual EtOH antagonists, some agents have indeed counteracted deep EtOH coma, but these results are relevant to heavy intoxications only. It is not clear which behavioural changes in the rat correspond to human inebriation after moderate doses of EtOH which is known to impair important abilities such as driving skills.

Interactions, synergism or antagonism, are usually classified as being pharmacodynamic or pharmacokinetic. Since acute EtOH inebriation is associated with rising blood alcohol concentrations (BAC), it is difficult to antagonize the socially accepted early part of inebriation without manipulating EtOH absorption. It is possible to close the
pylorus with various drugs (opiates, antimuscarinics, Al+++ ) and thus retard EtOH absorption (Holt & al. 1980). However, the consequences are unpredictable since EtOH is also absorbed via gastric mucosa and since the drugs used may interact with EtOH enhancing its effects on the central nervous system. There are animal data (Eskelson & al, 1976) to suggest that with an imidazoline derivative it is possible to lower BAC levels and antagonize EtOH intoxication by altering the EtOH distribution. However, these results have not been adequately confirmed and commonly accepted, and they are so far restricted to animals.

As to the late phase of inebriation, fructose in large doses (1-2 g/kg) is known to accelerate the disappearance of EtOH from the blood (Mezey 1976). Although the fructose effect has been demonstrated in man, it is not known how it modifies EtOH inebriation. It may not modify the acute inebriation of the absorption phase, nor does fructose eliminate hangover (Seppälä & al. 1976). However, it may help potential drivers to lower their BAC levels under the punisheable level. Briefly, it seems as if little is to be done to counteract acute EtOH effects by pharmacokinetic principles, and a search for pharmacodynamic EtOH antagonists remains important.

**Amphetamine and related drugs**

It seems logical to assume that various stimulants amphetamine included might counteract central depressant effect of EtOH. Despite this belief, relatively few properly designed studies have been conducted to document such an interaction in man (for references see Holloway & Holloway 1979). It follows that any claim for alleged drug-EtOH antagonism is difficult to accept or reject. The best policy may be to ignore such claims unless properly documented.

**Amphetamines** Generally, no antagonism by amphetamine of the EtOH (1.2 g/kg) induced impairment of human performance on balance, skipping, manipulation, pegboard, pursuit-rotor, or digit-span tasks was found after amphetamine 15 mg although performance on coding and mental arithmetic did improve (Wilson & Taylor 1966). Rutenfranz & Jansen (1959) showed in a small study that methamphetamine 9 mg corrected
the simulated driving performance impaired after EtOH 0.5 g/kg but did so only partially after EtOH 1 g/kg. The amphetamine dose should not be too large since Hughes & Forney (1964) and Newman & Newman (1956) failed to counteract EtOH with doses of 15–20 mg of amphetamine. In a carefully conducted study (Alkana & al., 1977) 50 mg of ephedrine sulphate reduced the effects of EtOH (0.8 g/kg) on EEG and coordination. In these circumstances ephedrine elevated BAC levels.

Dopaminergic drugs Long-term use of EtOH may enhance the turn-over of brain dopamine and noradrenaline (for references see Alkana & al. 1977). Attempts to antagonize EtOH effects with direct and indirect dopaminergic drugs have been done in animals and in man. Alkana & al. (1977) were able to demonstrate that l-Dopa taken as a single 1.5 g dose after drinking 0.8 g/kg of EtOH, significantly reduced the EtOH effect on EEG, motor coordination and divided attention in healthy male volunteers. The BAC levels were somewhat lowered after l-Dopa. The subjective feeling of inebriation as well as mental parameters did not change. In these experiments aminophylline 200 mg and ephedrine 50 mg also counteracted EtOH effects. The authors concluded that the EtOH antagonism may result from central noradrenergic activation. In a randomized double-blind clinical trial on alcoholics (Wadstein & al., 1978) no positive effects of treatment with apomorphine, or with the combination apomorphine+l-Dopa+carbidopa, on alcohol consumption or post-intoxication symptoms could be demonstrated. In fact the post-intoxication symptoms lasted significantly longer when the patients were on the combined treatment. These results are difficult to interpret in terms of acute EtOH antagonism, but they could refer to some EtOH–dopamine antagonism.

Coffee and caffeine

It is known that suitable doses of caffeine stimulate central nervous system increasing sleep latency, reducing total sleeping time, and improving various skills impaired by tiredness. Coffee and caffeine have therefore attracted attention as potential EtOH antagonists. However, good dose/response studies are rare. Franks & al. (1975) demonstrated that caffeine 300 mg given in decaffeinated coffee failed to alter
most parameters measured in a laboratory test battery, but it impaired the body balance slightly. After 0.75 g/kg of EtOH (BAC 0.9 mg/ml) caffeine did not antagonize the EtOH induced decrement of performance except in the reaction time tests. The antagonism was found both in visual and auditory reaction times. In a recent study Keuchel & al. (1979) reported that both EtOH (0.3 g/kg) and caffeine (150 mg) decreased concentration ability (an arithmetic test) in males, and the combined action was considered synergistic. For females, EtOH as well as caffeine improved concentration while the combination had an antagonistic effect. The authors emphasized the beneficial tranquilizing effect of EtOH in these tests; non-specific stimulation by caffeine may further impair the performance. In a study (Rutenfranz & Jansen 1959) where methamphetamine counteracted EtOH on driving skills, 200 mg of caffeine proved inactive.

Our group (Nuotto & al. 1979, unpublished) has recently done an interaction study on healthy male volunteers. In the first part, two different doses of decaffeinated coffee alone or fortified with 200 or 500 mg of caffeine were given after EtOH (1 g/kg) but they failed to antagonize the EtOH induced impairment of various psychophysiological measures as well as subjective inebriation. In the second part of the study done on the same subjects several months later, EtOH 1.5 g/kg impaired skills subjectively and objectively whilst 0.7 g/kg altered significantly lateral gaze nystagmus only. Administration of caffeine (250 + 250 mg) in decaffeinated coffee failed to antagonize the EtOH induced impairment significantly. A trend towards antagonism was seen after the first 250 mg dose given at rising EtOH concentrations. The absorption of caffeine was confirmed by gas chromatography which demonstrated dose-related caffeine concentrations in the serum. Very low and inconsistent serum caffeine resulted from decaffeinated coffee. The results show that in the tests used, caffeine is not an important EtOH antagonist and that increasing the caffeine dose does not improve the results. Nor may other coffee constituents counteract EtOH. The positive result by Alkana & al. (1977) with aminophylline 200 mg might depend on accidentally suitable dose ratios because qualitative differences between caffeine and theophylline are fairly small.
The caffeine–EtOH interaction may also depend on the test used. Forney & Hughes (1965) found no antagonism by caffeine 500 mg towards EtOH (0.5 g/kg) on verbal output, reverse reading and counting, and addition and subtraction, but they found an antagonism on colour differentiation, progressive counting and addition. Rosenfield (1960) antagonized EtOH (1 g/kg) effects on simulated driving with caffeine but this interaction was small. Nash (1966) antagonized with caffeine the EtOH induced impairment of memory for newly learned material.

Cholinergic drugs

Since smoking and drinking often belong closely together, there is much practical experience about the combined effects of nicotine and EtOH but not many good experiments in man. Myrsten & Andersson (1973) showed that smoking 5 cigarettes enhanced EtOH (BAC 0.65 mg/ml) action on the body balance and heart rate but counteracted EtOH effects on the simple and complex reaction time tasks. Smoking did not modify the EtOH kinetics in these circumstances. Smoking has also antagonized the EtOH induced impairment on visual discrimination (Tong & al.1974), choice reaction times (Lyon & al.1975), time judgement (Leigh & Tong 1976) and auditory attention task (Leigh & al.1977). In a recent study Knott & Venables (1979) showed that tobacco smoking (4 cigarettes) either prior to or during EtOH (BAC 0.7–0.8 mg/ml) consumption or both counteracted the EtOH induced slowing of alpha activity in EEG which was evident in both nonsmokers and smokers. Smoking failed to alter BAC levels significantly, which suggests that the observed antagonism occurs at the tissue level. Another example of central antagonism of nicotine and EtOH is the nicotine antidiuresis during EtOH diuresis; this interaction is well known in parties and also shown in animals where it bears correlation to blood and brain nicotine concentrations (Mansner & Mattila 1975). As to visual parameters, smoking tends to constrict retinal vessels and EtOH dilate them, and possible interactions measured must be interpreted with care.

Physostigmine is an old competitive inhibitor of specific and non-specific cholinesterase. During recent years it has drawn much attention as an antidote against the central antimuscarinic syndrome of
varying aetiology (antimuscarinics, antiparkinson drugs, phenothiazine neuroleptics, tricyclic antidepressants) which can lead in extreme cases in psychotic states. There are clinical data (Daunderer 1978) on more or less comatous drunken patients (BAC 2.5-4.8 mg/ml) who have transiently responded to iv or im injections (1-2 mg) of physostigmine given several times if needed. Physostigmine improved respiration and woke up unconscious patients to communicate or even move but it did not shorten the actual time of final recovery from the poisoning. The results from the physostigmine treatment in delirium states vary: Modestin (1974) found no response to 1-2 mg of it whereas Daunderer (1978) gave it repetitively at one-hour intervals and reached a good response in 6 out of 8 patients. The findings that physostigmine given iv (0.5-1.5 mg) may improve human memory (Davis & Yamamura 1978; Liljequist & Mattila 1979) and that the antimuscarinic effect may enhance the EtOH induced memory impairment (Liljequist & al. 1978) do encourage further experiments to counteract EtOH effects with physostigmine or other suitable cholinomimetics. It may prove wise to block peripheral muscarinic receptors with e.g. methylscopolamine in order to avoid unexpected cardiovascular collapses which actually occurred in one patient of Daunderer's (1978) material.

Various centrally active drugs

Doxapram is a non-specific central analeptic which has been reported to antagonize the central depressant effects of EtOH in dogs, rabbits and rats. Our group (Karhunen & al. 1978) has attempted to antagonize the effects of EtOH (1 g/kg) on psychomotor skills with iv doxapram (0.5 or 1 mg/kg). Doxapram 0.5 mg/kg injected after EtOH tended to enhance the EtOH induced impairment of coordination whereas the larger dose slightly counteracted EtOH on coordination and lateral gaze nystagmus. That dose of doxapram alone more or less impaired skills. The subjective effects of doxapram after EtOH were similar to or worse than the doxapram effects after placebo drink. Doxapram did not modify breath EtOH levels significantly. It seem as if drugs of this category do not offer particular benefits for counteracting acute EtOH inebriation.
Naloxone  There are animal data to suggest that a chronic administra-
tion of EtOH activates endorphin mechanisms in some way (Blum 1977). The concepts on endorphin mechanisms are much based on the antagonism of the effects observed by naloxone which is considered a specific pure antagonist for opiates. There are reports suggesting that drunken patients heavily intoxicated with EtOH (BAC 2.5-4 mg/ml) wake up from coma at least transiently after iv injections of naloxone (0.5-1 mg). However, the presence of opiates was not excluded or their presence was established (Sorensen & Mattisson 1978; Mackenzie 1979). Schenk & al. (1978) reported 4 patients with EtOH intoxication who showed a definite arousal reaction after large doses (4-28 mg iv) of naloxone. Normal pain threshold, the coordination and motoric ability as well as improved respiration could be found. No traces of opiates could be found in this material.

In experimental situation naloxone (0.4 mg) has also counteracted the EtOH (BAC 0.4 mg/ml) induced impairment of reaction times (Jeffcoate & al. 1979). This result is difficult to evaluate since so low doses of EtOH do not impair skills in all experimental situations. Our group (Nuotto & al., unpublished, 1980) has recently conducted a double-blind and cross-over study on healthy male volunteers administering EtOH (0.8 or 1.5 g/kg) and injecting naloxone (0.4 + 2 mg iv at 60 and 90 min) while the subjects showed early inebriation. The results await statistical analysis so far, but either dose of naloxone caused no fundamental changes in inebriation in terms of various skills. Instead the subjects reported less fatigue after naloxone injections in comparison with placebo injections. It may rather well be that habitual heavy drinkers do develop some deviations in the endorphin mechanisms and, consequently, they may respond to naloxone during the EtOH coma although healthy volunteers do not during a substantial inebriation. Since the dose of Schenk & al. (1978) were fairly high, a non-specific central analeptic activity of naloxone is not excluded although the common opinion is reluctant to accept that.

Lithium in "therapeutic" doses given to healthy volunteers over 14 days has impaired reactive skills but it tended to antagonize the EtOH (0.5 g/kg) induced impairment (Linnoila & al. 1974).
Neuropeptides There is evidence from animal experiments that thyrotropic releasing hormone (TRH) reduces the sedation, sleep, and hypothermia caused by various sedative agents EtOH included. Various mechanisms have been proposed for this analeptic action, one of the last being an inhibition of GABA systems (Cott & Engel 1977). The doses of TRH are so high that they are far beyond those needed for thyroid systems. Kraemer & al. (1979) demonstrated in rhesus monkeys that the effects of thiobarbiturate and TRH on an operant test were similar, excitatory or depressant depending the base-line behaviour of the individual, but when given together these two drugs acted as antagonists. A synthetic peptide histidyl-proline diketopiperazone, a putative active metabolite of TRH, reduces EtOH (4 g/kg) induced sleep in the rat (Prasard & al. 1977).

Our group (Linnoila & al., unpublished, 1979) has compared TRH and an "antiamnesic" hexapeptide Org 2766 as potential EtOH antagonists. The dose of EtOH (1.5 g/kg) was ingested within 45 min, Org 2766 was injected im (5 or 20 mg) at 1.5 hr, and TRH (10 μg/kg iv) 30 min later. A comprehensive test battery was administered before the EtOH intake and 2 min, 30 min, 1 hr and 2 hr after the TRH injection. Peptides alone slightly impaired objective psychomotor skills but the low dose of Org 2766 was experienced as a stimulant. When given after EtOH, either peptide failed to antagonize the EtOH induced impairment and even enhanced EtOH effects. TRH in particular was active in this respect irrespective of the parameter measured. One reason of this unexpected finding may be the fact that the breath EtOH concentrations were higher after peptides than after placebo injections, but some deviations from this mechanism was found on various tests. It seems as if in the doses used these interesting peptides do not offer an acceptable remedy to counteract acute inebriation.

Vitamins etc.

Excessive doses of water-soluble vitamins, particularly of the B group, have been widely used when cutting the drinking spells of chronic alcoholics. They may be valuable to compensate manifest of masked hypervitaminosis whilst the actual EtOH antagonism is less convincing.
Kelly & al. (1971) investigated it in a double-blind cross-over study on social drinkers of two age groups. They gave injections of placebo or vitamins C and group B iv before the subjects started drinking EtOH (0.72 g/kg). The vitamins did not modify the EtOH kinetics (peak BAC 0.8 mg/ml) which otherwise was similar in both age groups. But the vitamin injection reduced the subjective intoxication and improved objective performance particularly in the younger age group. The best antagonism was found in the reaction times whilst no significant change was found in the EtOH nystagmus. This suggests that the vitamins used are not really effective EtOH antagonists because the most sensitive parameter remained uninfluenced.

Pyritinol (pyrithiozone) is a pyridoxine derivative devoid of the B6 vitamin action. It has been used as "neurotropic" agent which may normalize or increase the glucose consumption in geriatric patients. In psychometric studies pyrithiozone has improved attention in a short-term task, and the "symptoms of cerebral decompensation" as well as general mental state may have been partly corrected by treatment with this agent (Lipton & al. 1978).

Krogh & al. (1978) have recently shown that pyrithiozone (7 mg/kg) antagonizes to some extent the EtOH induced changes in the auditory evoked potentials. EtOH (1 g/kg) alone reduced the N1-P2 amplitudes in the first part of the test and enlarged in the second part, as compared to placebo values. Pyrithiozone antagonized EtOH effects best when given after EtOH had been absorbed. Although this study demonstrates an EtOH antagonism at the electrophysiological level, the application of the data to practical behaviour and symptoms of inebriation is difficult. Comparison of the potential data with the results from psychomotor tests showed that the same tendency could be seen in the eye-hand test and two-hand tracing test but not in the simple reaction time test. Pyrithiozone and various "nootropic" drugs await further experiments in the EtOH antagonism topic.

Conclusions

Various attempts to counteract acute EtOH effects have not been very
rewarding so far. Various reports from animal experiments suggest that EtOH sleep or EtOH anaesthesia is effectively counteracted with various more or less non-specific stimulants, but these results refer to heavy EtOH intoxication only. An altered turn-over of various brain neurotransmitters well documented in animals may not be an important contributor to inebriation but is rather associated with EtOH inebriation in a non-specific way. One may conclude that there are no relevant animal behaviour model that matches the subtle central depression after low doses of EtOH. If EtOH acts as a solvent which impairs various membrane functions, a really effective specific antagonist would be hard to find. Minor antagonists are probable as reviewed above. In spite of this pessimistic view more research should be devoted to this important topic, particularly having chronic alcoholics as experimental subjects.

References


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