Drug Interactions involving Anticoagulants, Alcohols and Barbiturates

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(*A*) DRUG INTERACTIONS WITH ORAL ANTICOAGULANTS

Vitamin K is essential for the synthesis of prothrombin and other clotting factors synthesized in the liver (Factors VII, IX and X). Oral anticoagulants of the coumarin and indanedione series are competitive antagonists of vitamin K. Thus they are used to depress the blood prothrombin concentration to a point which is enough to prevent intravascular clotting but not enough to produce spontaneous bleeding. This critical prothrombin level can be upset by the concurrent administration of some drugs. Also if the dose of the anticoagulant required to produce the desired effect in a patient was determined when the patient was receiving another drug, withdrawal of this second drug may expose the patient to the danger of spontaneous thrombosis. Many drugs can interact with oral anticoagulants either to enhance or to reduce their activities.

1. Interactions with salicylates

It was mentioned in the previous article (1) that salicylates potentiate the anti-coagulant activity of the coumarins by their ability to displace the coumarins from protein binding. They are also potent antagonists of vitamin K, which action becomes important when salicylate is combined with oral anticoagulants.

2. Interactions with other anti-inflammatory agents (except steroids).

Phenylbutazone and other pyrazolone derivatives are known to enhance the action of coumarin and indandione anticoagulants. They are highly protein bound and will displace the anticoagulants from their protein binding. It is also possible that enzyme induction resulting in increased rate of metabolism of the anticoagulant can occur but this mechanism of action may not be important in man (2) Besides these actions, phenylbutazone is ulcerogenic in some patients and should be avoided during anticoagulant therapy.

Mefenamic acid or phenyramidol will potentiate the anticoagulant action of the coumarins and phenindione. The action of mefenamic acid is as a result of displacement of the coumarin and the phenindione from protein binding. But phenyramidol seems, from animal experiments, to act by inhibiting the hepatic enzymes responsible for the metabolism of these oral anticoagulants. Thus if these drugs must be given concurrently, the dose of the anticoagulant has to be reduced to obtain the desired prothrombin time.

3. Interactions with Steroids anabolic steroids and corticosteroids).

Many anabolic steroids e.g. methandrostenolone (Dianabol), oxymetholone (anadrol) have been reported to increase the action of phenindione and coumarin anticoagulants. This mechanism is not known but it has been suggested that this is due to increased affinity of the anticoagulant for the receptor site (4). This interaction has been shown to occur only with anabolic steroids that have 17-alkyl substitution. It will therefore not be expected to occur with nandrolone (Duraboline) and testosperone.

Adrenocorticotrophin (ACTH) and corticosteroids like cortisone and prednisone can increase the coagulability of blood and have also been shown to antagonise the anticoagulant effect of the coumarin when given together. Hence the dose of the anticoagulant has to be increased if it must be combined with these steroids.

Mixed oral contraceptive, norethynodrel and mestranol, has been shown to reduce the anticoagulant effect of bishydroxycoumarin (5) This is thought to be due to the oestrogen component which can cause a rise in the plasma levels of factors VII and X. The clinical significance of this **therapy** is not known. It is not known whether other oral contraceptives will have similar effect also.

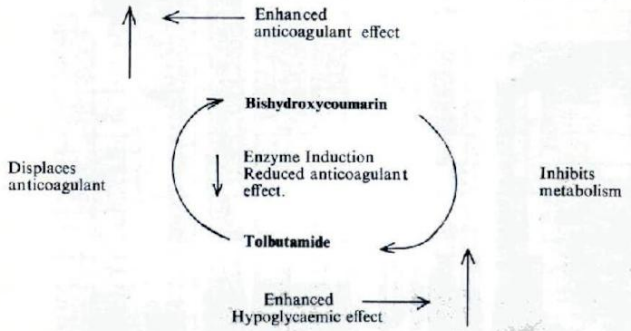
4. Interactions with Allopurinol (ant-gout agent)

Experiments in man and animals showed that allopurinol will increase the half-life of bishydroxycoumarin. This effect was though to be as a result of the inhibitory action of the allupurinol on the liver enzymes that metabolise the anticoagulant.

5. Interactions with oral hypoglycaemic agents.

It was reported that dicoumarol increased the serum level and prolonged the half-life of chlorpropamide in man (3) Experiments in animals (2) showed that tolbutamide will initally enhance the anticoagulant activity of the coumarins by displacement from protein binding. It can also induce increased activity of the anticoagulant metabolising enzymes in the liver and thus antagonise its initial hypoprothrombinaemia. These observations in animals may not apply to man since tolbutamide is rapidly metabolised in man and may not reach a concentration high enough to cause any significant displacement of the anticoagulant from protein binding.

It was also shown that bishydroxy-coumarin can increase the half-life of tolbutamide. This was though to arise from inhibition of tolbutamide metabolising enzymes. Thus two drugs administered concurrently can produce two different types of drug interactions at the same time (see illustration below). Phenindione did not seem to produce the effect on tolbutamide.



6. Interactions with hypnotics, sedatives and tranquilisers

Barbiturates increase the rate of metabolism of the coumarins by inducing an increased activity of the liver microsomal enzymes. Thus they will reduce the effect of the anticoagulant. This action of barbiturates is seen even with small doses. Both human and animal studies, indicate that the interaction will be evident within 2-5 days of therapy. Also after withdrawal of the barbiturate, normal enzyme activity is restored in 2 to 3 weeks.

No interaction with anticoagulants has been reported with benzodiazepines (e.g. chlordiazepine, diazepam, oxazepam, nitrazepam) and these may be useful alternatives to barbiturates where a combination must be given.

Glutethimide seems as active as barbiturates in stimulating the microsomal enzymes and can reduce the action of anticoagulants.

Haloperidol and ethchlorvynol have all been shown to reduce the effect of anticoagulants. The mechanisms of action are not known.

There has been conflicting reports about the interaction of chloral hydrate and the related drugs (*e.g.* chloral betaine and petrichloral—hydrolysed to chloral in the stomach, and triclofos) with anticoagulants (4). These drugs are metabolised to trichloroacetic acid which is strongly protein bound and will enhance the action of coumarins by displacing them from protein binding. It has also been reported that chloral hydrate reduces the anticoagulant effect of coumarin. This was thought to result from stimulation of the microsomal enzymes in the liver. These conflicting reports may indicate that caution must be taken in concurrent administration of chloral hydrate and anticoagulant.

Dichloralphenazone (a complex of chloral and antipyrine) reduces the anticoagulant effect of coumarins. This effect of dichloralphenazone is attributable to the antipyrine component which probably masks the effect of the chloral. Experiments in animals and man indicated that the reduced anticoagulant effect is due to stimulation of coumarin metabolising enzymes.

7. Interaction alcohol

No interaction has been known to occur between anticoagulant and normal amount of alcohol. This situation is different with heavy drinkers or in people with impaired liver function. There is evidence that—in heavy drinkers, hepatic enzyme induction can occur leading to reduced effect of the anticoagulant.

8. Interaction antibiotics

Some antibiotics are believed able to enhance the effect of oral anticoagulants by interfering with the production vitamin K by microorganisms in the gut. But the gut synthesis of vitamin K is an important source of the vitamin only when the dietary content is particularly low.

However, chloramphenicol can enhance the action of anticoagulant probably by inhibiting the hepatic enzymes responsible for the metabolism of coumarins. Chloramphenicol may also inhibit the synthesis in the liver of blood clotting proteins. Clinical importance of this is not known.

Griseofulvin will, in some patients, reduce the anticoagulant effect of coumarin. It is postulated that griseofulvin may be acting as an enzyme inducer and thus enhancing the metabolism of the coumarin.

9. Interaction with antilipaemic agents (e.g. clofibrate)

Clofibrate has been shown to enhance the action of warfarin and phenindione. This does not occur in every patient. However, whenever a clofibrate and an oral anticoagulant are to be given concurrently, the possibility that the dose of the anticoagulant may need to be reduced must not be overlooked. The mechanism of this interaction is not known but it has been suggested that clofibrate increases the affinity of the anticoagulant for its receptors in the liver.

10. Interaction with thyroactive agents

Dextrothyroxine will enhance the activity of warfarin. It is thought that the dextrothyroxine acts by increasing the affinity of the anticoagulant for the receptor site. It is recommended that when dextrothyroxine is to be given during anticoagulant therapy the dose of the anticoagulant should be reduced by 1/3 and then later readjusted according to laboratory findings.

11. Interaction with Phenytoin

Phenytoin has been reported to reduce the anticoagulant activity of dicoumarol probably by enzyme induction. It has also been shown that dicomuarol can enhance the actions of phenytoin by inhibition of the enzyme responsible for phenytoin metabolism.

(*B*) DRUG INTERACTION INVOLVING ALCOHOL

Many people take alcohol in one form or the other. It is therefore necessary to know which drugs are likely to interact with it.

The type of interactions which can occur when alcohol is combined with another drug may at times depend on whether the person is an alcoholic or not.

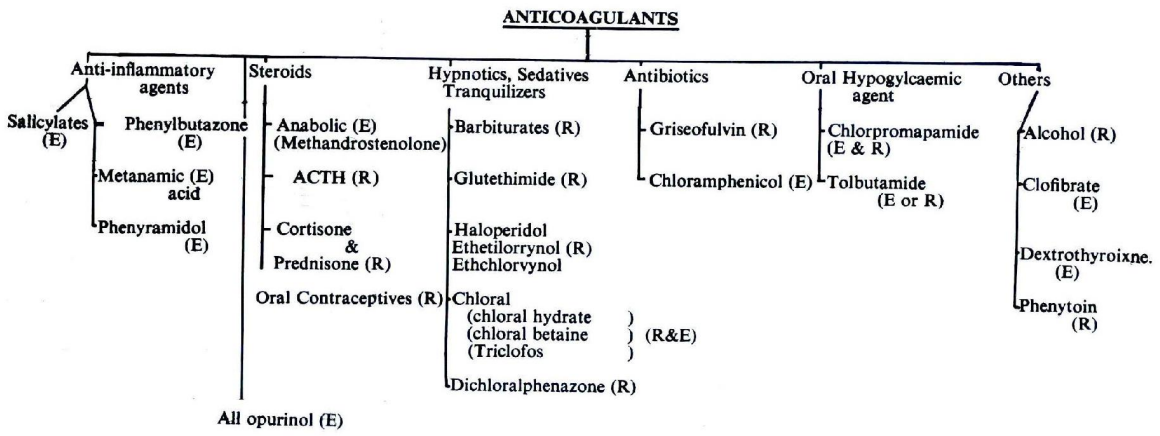
1. **Interaction with disulfiram**

Alcohol is normally converted to acetaldehyde by alcohol dehydrogenase. The aldehyde dehydrogenase then converts the acetaldehyde to acetic acid which is further metabolised to cabon dioxide and water. Disulfiram inhibits the aldehyde dehydrogenase and thus prevents the breakdown of acetaldehyde. This means that acetaldehyde will accumulate in the body if alcohol is taken with disulfiram. The aldehyde produces very unpleasant effects and can cause death. This interaction of disulfiram with alcohol is the basis of the treatment of alcoholics with disulfiram.

2. **Interaction with Metronidazole**

It has been shown that metronidazole will interact with alcohol by a mechanism similar to that of disulfiram. Hence patients are advised not to take alcohol while on metronidazole therapy. It is not known for certain but

SUMMARY OF DRUG INTERACTIONS WITH ORAL ANTICOAGULANTS



KEY: E = Enhanced anticoagulant activity
R = Reduced anticoagulant activity

probably quinacrine will interact in a similar way with alcohol.

3. **Interaction with barbiturates**

Alcohol is a CNS depressant and when combined with a barbiturate will potentiate the sedative or the hypnotic effect of the barbiturate. This does not seem to be simple additive effect of the two depressant drugs. The mechanism of this interaction is not known but it is thought that probably alcohol increases the membrane permeability of CNS cells to barbiturates.

Barbiturate can also potentiate the effect of alcohol. In one experiment (6) on the effect of alcohol and phenobarbitone on the typing performance, it was shown that after phenobarbitone the typing was slower but more accurate than after the dummy treatment. After alcohol, the typing was faster but less accurate. When both alcohol and phenobarbitone were combined with half doses of the above, the effects observed were those of alcohol as above but greater than alcohol alone.

It is also known that alcohol can stimulate or inhibit the activity of liver enzymes depending on how it is used, Decreased sensitivity to the sedative (barbiturate) and also to alcohol has been shown to occur in chronic alcoholics. The decreased sensitivity is due to increased liver enzyme activity. In non-alcoholics, high concentration of alcohol will inhibit liver enzymes and therefore enhance the action of drugs administered concurrently.

4. **Interactions with non-barbiturate hypnotics.**

Chloral hydrate, paraldehyde, glutethimide, will all show enhanced depressant effect with alcohol. It is not unlikely that the effects of other such hypnotics will be enhanced by alcohol.

5. **Interaction with Tranquiliser**

There is evidence that tranquilisers like phenothiazines, reserpine and meprobamate but not the benzodiazepines will interact with alcohol to produce, enhanced CNS depression. This depression may be more than the simple sum of depressant effect of the combination.

6. **Interactions with Antidepressants:**

There are a few reports about interactions of monoamine oxidase inhibitors with alcoholic drinks. It is thought that such interactions are not attributable to alcohol but to tyramine which is present in some alcoholic beverages as the symptoms resemble the well known reactions of tyramine (in cheese) with MAO inhibitors. Since it is not easy for a patient to know which alcoholic drinks contain tyramine, it is best to warn patients to avoid alcohol during MAO therapy.

Some tricyclic antidepressants like amitriptyline will enhance the effects of alcohol. It does not seem all tricyclic antidepressants will do this but it is wise to warn patients against alcohol while on tricyclic antidepressant therapy.

7. **Hypoglycaemic agents.**

It is usual to advise diabetics not to take alcohol because of its high calorie content. Alcohol seems able, at least, because of its calories content, to enhance the action of insulin and the oral hypoglycaemic agents.

Chlorpropamide has been reported to produce disulfuram—type of reaction with alcohol. This will probably occur to a certain extent with other sulphonylureas but not with the biguamides.

In heavy drinkers, alcohol seems to produce liver enzyme induction and this will reduce the half-life oral hypoglycaemic agents except acetohexamide. However in moderate drinkers alcohol will enhance the effects of the hypoglycaemic agents.

8. **Oral Anticoagulant**

Alcohol stimulates the liver Microsomal enzymes that metabolise warfarin and thus will reduce the half-life of the anticoagulant. This effect is only seen or important in alcoholics.

9. **Phenytoin**

Alcohol can reduce the half-life of phenytoin in heavy drinkers by means of liver enzyme induction. The effect of alcohol in moderate drinkers is not reported.

10. **Tetrachloroethylene**

This drug is used as an anthelmintic and should not be absorbed. It is thought that alcohol will lead to the absorption of the drug and this will cause serious CNS depression.

(*C*) DRUG INTERACTIONS INVOLVING BARBITURATE (PARTICULARLY PHENOBARBITONE)

Chronic administration of a drug can reduce the pharmacological effects of that drug or of another drug by increasing the activity of metabolising enzymes in the liver microsomes. Phenobarbitone can stimulate not only its own metabolism but that of some drugs given concurrently with it.

1. **Steroid hormones.**

Phenobarbitone is known to increase the metabolism of steroid hormones. It will therefore increase the metabolism of oral contraceptives—oestrogens and progestogens. This effect does not seem to be of any clinical importance. It has been reported that phenobarbitone decreased the half-life of prednisone or dexamethasone. This interaction is important in an asthmatic patient who has been taking phenobarbitone but requires a steroid for an effective relief.

2. **Digitoxin**

It has been reported that phenobarbitone can increase the rate of metabolism of digitoxin probably by microsomal enzyme induction. It may therefore be necessary to increase the dose of digitoxin when it has to be given with phenobarbitone.

3. **Diphenylhydantoin**

Phenobarbitone will increase the metabolism of the diphenylhydantoin by enzyme induction. This is not important since phenobarbitone has also an anticonvulsant activity.

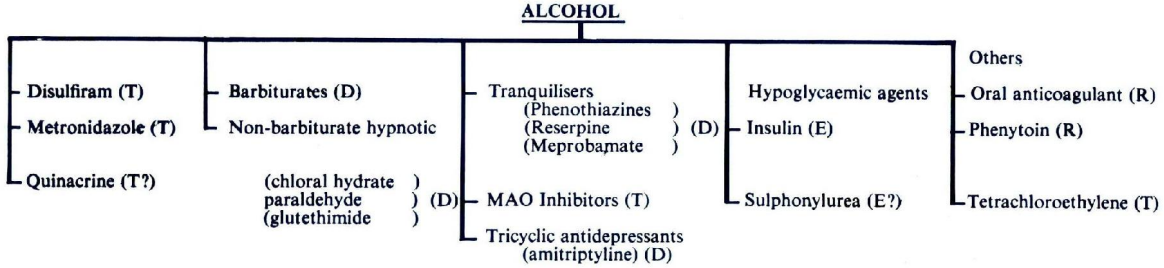
4. **Bilirubin**

In kernicterus, there is a high serum level of unconjugated bilirubin. Phenobarbitone is used in this condition to stimulate the formation in the liver of glucuronide and thus reduce the bilirubin level in the blood.

5. There are other drugs whose metabolism can be enhanced by phenobarbitone viz

Warfarin and bishydroxycoumarin
Aminopyrine
Cortisol

SUMMARY OF DRUG INTERACTIONS WITH ALCOHOL



KEY

T = Toxic effects

D = Enhanced CNS depression

E = Alcohol enhances the effect of the drug

R = Alcohol reduces the effect of the drug.

Criseofulvin
Hexabarbitone
Phenylbutazone
Testosterone
Zoxazolamine
Methyldopa

The mechanism involved in these interactions is liver microzomal enzyme induction.

SUMMARY OF DRUG INTERACTIONS WITH BARBITURATES

Phenobarbitone will enhance the metabolism of the following:

Steroids — Oral contraceptives (?)
Testosterone
Prednisone
Cortisol
Digitoxin
Diphenlhydantoin
Warfarin and bishydroxy coumarin
Aminopyrine
Griseofulvin
Hexobarbitone
Zoxazolamine
Methyldopa
and the exretion of Bilirubin

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