Drug Interaction

The Scientific Basis of Medicine

Presented by Professor Colin Dollery, Dr Matthew Conolly and Dr Donald Davies.
Introduced by Dr Ian Gilliland.

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<Opening titles>

<Gilliland to camera>

Professor Dollery is Professor of Clinical Pharmacology at the Royal Postgraduate Medical School, and Physician to Hammersmith Hospital. His initial research work was connected with hypertension and its treatment and received international attention and regard. His research standing has led to him being Secretary of the European Society of Clinical Investigation. He has built up an immensely active department, interested in all aspects of clinical pharmacology, and two members of his staff, Dr Conolly and Dr Davies, will take part in this presentation on drug interaction. Professor Colin Dollery.

<Dollery narrates over film with shots of: dispensary sign; patients in waiting area of dispensary department of hospital; medicines on pharmacy shelves; close-up of prescription>

When a patient sees a doctor they very frequently receive a prescription for a drug. A recent survey in this hospital showed that only 12 % of patients were not given any drugs in the previous 24 hours. And 4 out of 178 had received more than 10 different drugs in that short time. This pharmacy stocks about 2400 different drugs in dosage forms – allowing for different formulations, about 1000 different chemical substances. Yet, this is a hospital with a reasonably restrictive policy about stocking drugs. Many have more than this one. If each patient receives an average of 5 drugs, it's easy to work out that there are about 10^{15} possible combinations. If only a minute proportion of these combinations significantly modify the action of one member of the combination, there would still be a mind-boggling number to try to remember. And drugs do interact in many different ways.

This prescription contains a potential interaction. It is impossible to try to memorise all of the possibilities and the purpose of this programme is to suggest a way of handling the problem by a combination of common sense, pharmacological and pharmacokinetic knowledge.

<End of film clip>

<Dollery to camera in studio>

First, the common sense. Look out for problems with drugs that are used to treat serious diseases, particularly with drugs that have a small therapeutic ratio, that's a small difference between the dose that has a desired effect and that which may have a toxic effect; and particularly drugs that have a steep dose response curve.

Now, the second and third parts of this involve a consideration of pharmacological and pharmacokinetic knowledge. And to understand that we must first go to a model and see what happens to a drug after it enters the body.

<Dollery walks to display board, refers to diagrams and narrates over them, interspersed with talk to camera>

The symbol I'm using for a drug is this, a circle with a bit bitten out of it. Let's consider what happens when a drug is given by mouth. The drug passes down the oesophagus into the gut, and an interaction may occur here, for example, divalent cations like iron salts or calcium salts combine tetracycline and prevent it being absorbed. But on the whole this is not a very important site of drug interaction. Now, after the drug has been absorbed, it will pass up the portal blood and into the liver. This shows the drug molecule in the liver. Now, the liver is a very important site of drug interaction because it's an important site of drug metabolism. Many different drugs are metabolised here, particularly to a hydroxyl derivative, and I've shown that by inserting a hydroxyl derivative on this drug molecule. These hydroxylated derivatives are usually pharmacologically inactive, so this is an important way of inactivating a drug. But, even more important than that, the rate at which this occurs can be modified by the presence of another drug, either slowed down or speeded up. And so this is a very important source of drug interaction and one that Dr Davies will be talking more about later on.

Well, then the drug passes through the liver, along through the plasma; and many drugs, particularly acidic ones, are transported in the plasma, bound to serum albumin, and that's shown by the drug here occupying a binding site on the albumin molecule. A drug like warfarin is about 99.9 % bound to albumin. Now, if another drug comes along – it could be clofibrate or phenylbutazone – that has an even higher affinity for the binding site, it will displace the drug from its site on the albumin, make more drug available free in plasma, and since it's the free drug that usually exerts the pharmacological effect, it will cause a temporary but quite large increase in that pharmacological effect. But note it can only happen once. Once the drug has been displaced from the albumin molecule, there isn't any more left there to be displaced, so this is a once for all, a short-lived effect.

And then the drug will pass along, still in the bloodstream, until it reaches its site of action. Here I've shown it acting upon a tissue cell, and there it will act upon the receptors upon the cell and bring about the drug's effect. But suppose that some of those receptors are already occupied by another drug that can occupy the receptors but doesn't have the effect, then that means the effect will be lessened. And we call that effect competitive antagonism. And there are many examples of that where an antagonist occupies the receptor, prevents the drug gaining access to the receptor and thereby diminishes its effect.

Well now, that's a fairly complicated way of looking at things and there is one great simplification that can be made and it's this: we can look upon interactions as basically being of only two kinds, the first kind that modify the amount of drug reaching the site of action, so those would be interactions in the gut, in the liver and in the plasma because they all modify the amount of drug reaching the site of action, and, indeed, have an effect rather similar to the dose being changed. The second kind of interactions are those which occur at the site of action and these do not depend upon a modification of the amount of drug reaching the site of action but upon the effect that it has when it reaches it. Now, why is that important? Well, it's important for this reason: that the first kind of interactions, the ones that modify the amount getting there, cannot be predicted from a knowledge of pharmacology but they can be predicted from a knowledge of pharmacokinetics, the science of what happens to drugs in the body. Whereas once one gets to the site of action, these interactions can be predicted from a knowledge of pharmacology. So, by combining a knowledge of pharmacokinetics and pharmacology, we can gain an understanding of drug interactions. And now Dr Conolly is going to discuss the second type, the kind of interactions that occur at the site of action, the ones which we can understand through pharmacological mechanisms.

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<Conolly to camera>

As Professor Dollery has said, drugs may interact with one another at the receptor on the cell surface. One is very familiar with this phenomenon in classical pharmacology, although within the clinical setting examples are less common. One example would be nalorphine whose action can partially be explained on the basis of competitive antagonism towards the opiates at a cell surface receptor. Use is made of this interaction in several circumstances of which perhaps the most important is the treatment of respiratory depression in the newborn infant when the mother was given opiates late in labour. However, it would be wrong to think of this type of interaction as occurring only at cell surface receptors. It may occur, for instance, when two compounds compete with one another for binding to active sites on an enzyme molecule. Let us take as an example the drug allopurinol

<Conolly refers to diagram and narrates over it>

Allopurinol is known for its ability to antagonise the action of the enzyme xanthine oxidase. Xanthine oxidase, of course, normally catalyses the degradation of hypoxanthine, through xanthine to uric acid in which form it is excreted. We'll represent blockade of enzyme action with these white bars. However, this is not the only action which xanthine oxidase is responsible for. And on the bottom of the chart, you will see a further very important degradation in which this enzyme takes part and that is the degradation of 6-mercaptopurine to 6-thiouric acid. And this reaction too is antagonised by allopurinol.

<Conolly to camera>

It not infrequently happens that a patient who is receiving 6-mercaptopurine may be hyperuricaemic and require to be given allopurinol. However, if this combination of drugs is to be used then the clinician responsible must do two things. Firstly, the dose of 6-mercaptopurine must be reduced, perhaps to as little as 25 % of the original dose, and secondly, the effect of 6-mercaptopurine on bone marrow function must be very closely monitored and failure to take these precautions has resulted in death from marrow aplasia.

The second example is somewhat different. Insulin is a vital drug in the treatment of many diabetes. We accept its blood-sugar lowering properties whilst taking for granted the mechanisms which often come into play to prevent or to ameliorate undesirable falls in the level of blood glucose. These mechanisms are largely dependent upon beta-adrenergic activity. And the advent of beta-blocking drugs has brought to light a somewhat troublesome kind of drug interaction where drugs have opposing actions on a common physiological mechanism.

<Conolly refers to series of diagrams and narrates over them, interspersed with talk to camera>

In the first part of this illustration, we can see the fall in blood glucose which occurs when a patient is given an injection of insulin. The compensatory mechanisms that I've mentioned then come into play and the blood sugar level starts to rise back towards normal. Contrast this panel with that on the right hand side showing what happens when a patient is given, in addition to the insulin, a small dose of propranolol. The changes which take place are now shown by the black line. First of all, the fall in blood sugar is significantly greater and, secondly, the rate of rise of the blood sugar back towards normal levels is significantly slower. <*To camera*> And troublesome hypoglycaemia has been experienced as a result of this type of drug interaction.

And now for something completely different. I ask you to cast your mind back to that shot of the prescription that was shown earlier in this programme, because the example that I now want to consider is of something which happens when one drug alters some aspect of the pharmacodynamic behaviour of another. Now this, of course, can happen in many ways such as changing absorption, protein binding, or influencing the rate of elimination from the body. This particular example is the interaction between the tricyclic antidepressant drugs and adrenergic neurone blocking drugs used in the treatment of hypertension. And in this particular instance, the drug in question is bethanidine.

<*Next graph*> The first part of this figure shows how mean arterial pressure is reduced as bethanidine is introduced into the patient's treatment in step-wise increasing doses. At this point in time, two doses of 25 milligrams of desmethylimipramine are given to the patient. And you can see that there is a rapid loss of pressure control, the mean arterial pressure rises back to pre-treatment levels. And despite the fact that bethanidine is continued in an unchanged dose for several more days, it is some eight days before pressure control is regained. The explanation for this unwanted drug interaction is to be seen in the next diagram.

<Conolly walks to display board, refers to a diagram and narrates over it, interspersed with talk to camera>

Bethanidine and drugs like it have their action by being concentrated in the peripheral terminal of the adrenergic nerves. They gain access to this site by being carried in by a mechanism known as uptake 1. Uptake 1 is normally there to restore noradrenaline once it has been released into the synaptic cleft for transmission of an adrenergic nerve impulse. With high concentrations of these drugs within the nerve terminal, transmission of the nerve impulse is blocked.

Now, the tricyclic antidepressants have the ability to block this uptake mechanism and, indeed, this is probably the reason why they exert their antidepressant effect. We will illustrate this blockade in this fashion <*adds labels to diagram*>. As far as the peripheral sympathetic nerves are concerned, the effect of this blockade is to prevent bethanidine gaining access anymore to the nerve terminal. And the result is that once the bethanidine that is already within the nerve terminal becomes dissipated then the nerve impulse, once more, becomes transmitted in the normal manner, and the result of this, as you saw in that previous diagram, is that pressure control is lost.

Now, it does appear that this antagonism at the level of the neuronal uptake 1 is a competitive one and therefore it may be overcome simply by increasing the dose of bethanidine. But the important thing here, as in all the examples we have been considering, is to be aware of the possibility of such an interaction taking place at all.

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<Davies to camera>

Professor Dollery has already told us that drug action depends not only on the intrinsic activity of the drug but also upon those factors which control the concentration of drug at receptor sites. Thus the rate of elimination has a great influence on the action of a drug.

<Davies refers to series of diagrams and narrates over them, interspersed with talk to camera>

Drugs of high lipid-solubility readily cross biological membranes as shown by the black arrows here. They cross the gut wall, they cross the blood-brain barrier, but they also cross the renal tubular wall and therefore excretion in the urine is insignificant. How are such drugs excreted from the body? In most cases they are transformed in the liver to less lipid-soluble, often inactive metabolites, shown by the white arrows here, which can be excreted in urine. Thus the rate of elimination, and therefore the duration of action of a lipid-soluble drug, will depend on its rate of metabolism in the liver.

With drugs which have to be almost completely metabolised to be eliminated, there is great scope for drug interactions. A vast number of drugs and other chemicals can alter the activity of the drug metabolising enzymes in the liver. <*To camera*> This is particularly true for the enzymes which catalyse the oxidation of drugs, and for the remainder of my presentation, I want to concentrate on this one route of metabolism.

In the endoplasmic reticulum of liver cells, there is an enzyme system which activates molecular oxygen and this active oxygen oxidises drugs. The terminal oxidase is a cytochrome called cytochrome P450. <*Next diagram*> Here is a simple version of the mechanism of oxidation of drugs. The drug D combines with the cytochrome P450, with the cytochrome in its oxidised form. The cytochrome is then reduced by an enzyme which I have called NADPH P450-reductase. The reduced

cytochrome can combine molecular oxygen to give an active oxygen complex, which breaks down to give oxidised drug with the oxidised cytochrome being recycled.

There is almost certainly more than one type of cytochrome P450, possibly two or three but no more. However, there are hundreds of drugs which are substrates for this enzyme system. Therefore each cytochrome must catalyse the oxidation of a very large number of drugs. It is because of this apparent lack of substrate specificity that so many interactions occur with this enzyme system. For example, one drug may inhibit the oxidation of another drug by acting as an alternative substrate. It can compete for binding sites here on the cytochrome or for electrons from NADPH or active oxygen here.

<*To camera*> To add to our problems, a large number of drugs can, over a period of days or weeks, increase the activity of this oxidising system in the liver of humans. The exact mechanism of this so-called enzyme induction is not established. In studies with laboratory animals, it was shown with the prototype inducing agent phenobarbitone that there was both an increase in the synthesis and a decrease in the catabolism of components of the liver endoplasmic reticulum, including cytochrome P450. The net result was an increase of two- or threefold in the rate of oxidation of drugs.

What then are the therapeutic consequences of changes in rates of oxidation of lipid-soluble drugs? The next chart is a computer simulation of a particularly unfortunate patient. <*Next graph*> Plasma concentration is plotted here, and the time along the horizontal axis. When a drug is given 3 times daily, a proportion is lost between doses. That proportion depends on the dosing frequency and the plasma half-life of the drug. Drug will accumulate in this case because the dosing frequency is one fifth of the plasma half-life. We reach a steady state of plasma concentration here where the input equals the output. If at this point, an inducing agent was introduced, there will be, after a delay of a few days, an increase in the rate of oxidation of the drug. More drug will be lost between doses and the plasma concentration will fall to a new steady state plasma concentration. Withdrawal of the inducing agent will allow, after a few days, the plasma concentration to return to its pre-induced value, that is when

the enzymes have returned to their normal values. At this point the patient is given an inhibitor which immediately increases the plasma half-life of the drug by inhibiting its oxidation in the liver. There's a rise in the plasma concentration to a new high steady state value. This concentration would fall on withdrawal of the inhibitor. This is not shown here.

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<*Davies to camera*> So much then for the theoretical patient. This is what can happen in practice. This chart shows the plasma concentration and the thrombotest of a patient taking the oral anticoagulant drug warfarin <*next graph*>. This patient was studied by Drs Breckenridge and Orme in our department. On a dose of 4 milligrams daily, the concentration was 4 micrograms per ml and there was good anticoagulant control for the first 20 or so days. At this point, Welldorm, or dichloralphenazone, a hypnotic was introduced. This increases the activity of the drug-oxidising enzymes. There's a fall in the steady state plasma concentration of the drug with a corresponding loss of anticoagulant control. Withdrawal of Welldorm the inducing agent will, after a few days delay, allow the concentration to rise with a regaining of the anticoagulant control.

Now, if the doctor had been unaware of the introduction of an inducing agent and no plasma concentration measurements had been made, he would have been tempted at this point to increase the dose of warfarin to regain control. Had he done so, this would have been perfectly all right providing that the patient continued to take the inducing agent, Welldorm. If, however, after increasing the warfarin dose, the inducing agent was stopped, the plasma concentration would rise to very high values and there could be very serious consequences.

<*Next graph*> My final chart shows another patient taking, again, warfarin orally, this time in a dose of 3.5 milligrams daily. <*Indicates plasma warfarin results*> Concentration 3 micrograms per ml, good anticoagulant control for the first 40 or so days. At this point, anticoagulant control was lost and there was a corresponding fall in plasma concentration. Questioning of the patient revealed that, at this point in

time, he had on the advice of his doctor stopped drinking alcohol. Thus a possible explanation of these results would be that alcohol inhibits the oxidation of warfarin and therefore there was a fall in plasma concentration. This was confirmed when the patient was re-challenged with alcohol at this point here. Alcohol was introduced and you see there's a rise in the plasma warfarin concentration with a corresponding change in anticoagulant control, and at this point the patient had a nose bleed.

<Davies to camera>

I should add that this may not be a simple case of inhibition because the patient also had a slightly abnormal liver. However, this example does serve to illustrate that almost any foreign chemical introduced into the diet may affect the rate of oxidation of lipid-soluble drugs and therefore their response.

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<Dollery, Conolly and Davies seated for discussion to camera>

<Dollery>

We've discussed some of the more important mechanisms of drug interactions in man and we must now discuss the clinical significance and importance of them. I'll turn first and ask you, Matt, the kind of drug interactions you've been discussing, can you give any guidance as to the situations where one should be particularly on the look out for them?

<Conolly>

Well, I think apart from making the obvious truism that one's obviously going to get drug interactions when patients are taking large multiple numbers of drugs, I think the sort of circumstances which are likely to give rise to important drug interactions are when a patient is taking drugs which have a very steep dose response curve. I think it's really no coincidence that the examples that I discussed earlier on are those

where things like the patient's blood pressure or the patient's blood sugar are being regulated by drugs, where relatively small change in the drug dosage or disposition is going to produce a large physiological change, then we might expect to see quite significant effects from any drug interactions occurring. And, of course, as one might expect, when drugs are ones which depend for their elimination on metabolism then, of course, they're laid open to a whole lot of different mechanisms of interaction which Donald has already touched upon.

<Dollery to camera, then off-camera>

Well, Donald, that does bring us to you. You ended with a rather daunting message to the effect that almost any drug or chemical substance – I think alcohol was the example you used – could affect the rate of metabolism and thereby cause drug interactions. Now, if that is the situation, then can any insecticide or food additive besides any over-the-counter medicine cause drug interactions or can you tie it down a bit more and give rather more specific guidance about the situations which are most likely to give trouble?

<Davies>

Well, in fact, an insecticide can, DDT increases the rate of oxidation of drugs, but let's tie it down a little. I think that, first of all, we have to think of the drug itself. If it is extensively oxidised, we must look after interactions. Now, what about the drugs which alter the rate of oxidation? They usually are themselves oxidised in the liver and they're usually very fat soluble. That really is all we can say about the ones causing the interactions. Possibly, it is easier to think in terms of drugs which do not cause interactions rather than trying to remember the ones that do.

<Dollery>

Well can – you spoke about anticoagulants for example – can you tell us, perhaps, one or two of those that do and any that we know that don't?

<Davies>

Well, this is a good subject because it's been well researched. The introduction of a hypnotic to somebody on an oral anticoagulant, as you saw, is potentially dangerous. Hypnotics such as amylobarbitone and dichloralphenazone do affect the rate of oxidation of oral anticoagulants. Some work done in our department by Dr Breckenridge shows that nitrazepam, on the other hand, which is given in very much smaller doses, does not affect the rate of oxidation of warfarin and therefore can be safely taken with warfarin without loss of anticoagulant control.

<Dollery>

Is that a guideline then? Can you say if the drug is only given in a small dose that it won't cause this effect whereas drugs given in large doses of hundreds of milligrams or grams will?

<Davies>

I think it possibly is a guideline. We don't really have enough information for me to state categorically that that is so.

<Dollery>

Well, thank you very much. Well, in this programme we've dwelt upon interactions, particularly where the mechanisms are known because those are the easiest to understand. But one must remember that there are other interactions of a much less specific kind and the prescription that's shown on the monitor now illustrates an example of this […]

<Dollery narrates over slide>

[…] that occurred in our own clinical practice lately: a patient admitted to hospital, who had got thalamic pain, and it had been decided to give a trial of treatment with

Carbamazepine, Tegretol. His pain was very bad and the regular house physician was not on duty and the relief man seeing him – and the patient was complaining a lot – successively prescribed chlorpromazine, then diazepam both intravenously and intramuscularly, and then finally in the early hours of the morning, heroin, diamorphine. And by the time our own house physician came back on duty next morning, the patient was really quite ill. He was nearly comatosed, he was drowsy, he had a flapping tremor, he was ataxic and dysarthric. In fact, the house physician thought he must have suffered an infarction of his cerebellum. But really all that had happened was he was poisoned, and he was poisoned by the multiplicity of drugs, which, apart from having many different pharmacological actions, all shared in common a depressant effect upon the central nervous system. That is the final message, I think, to leave with you that if you are giving a lot of different drugs that do share an action in common, then it is likely that there will be an additive effect: in depressing the central nervous system, in lowering the blood pressure, these kind of things. So, if one thinks about what you're doing, tries to keep the number of different drugs that are prescribed at the same time down, and knows something about pharmacokinetics and something about pharmacology, the problems with drug interactions can be controlled.

<End credits>