MEDICAL PRACTICE

Today's Treatment

Drug-induced diseases**Drug-induced cardiovascular disease**

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Adverse reactions to any group of drugs can be divided into those that occur as an exaggerated but otherwise normal response to the drug and those that represent aberrant effects unrelated to its therapeutic action. This review of drug-induced cardiovascular disease will deal principally with the second type of adverse reaction and will not discuss, in any depth, problems such as postural hypotension caused by antihypertensive agents, clinically important as they may be. In any survey of drug-induced disease cardiovascular drugs are among the commonest agents incriminated. The most frequent drug-induced cardiovascular disorders are probably cardiac arrhythmias, heart failure, changes in blood pressure, and vascular spasm.

Drug-induced arrhythmias

Paradoxically, the commonest drugs to cause cardiac arrhythmias are those that are themselves used to treat rhythm disturbances. Although the incidence of digitalis-induced arrhythmias has decreased because of the wider use of potent diuretics in treating heart failure, these are still a source of concern, especially in elderly patients and those with compromised renal function. Virtually every type of arrhythmia, both ventricular and supraventricular, has been described with digitalis. The most worrying are ventricular ectopics occurring in runs, which may merge into short bursts of ventricular tachycardia or fibrillation.

Even atrial fibrillation, itself an indication for digitalis treatment, may be a sign of overdose. As with any other suspected digitalis-induced arrhythmias, drug withdrawal is advisable, and potassium should be replaced when necessary. If life threatening the arrhythmia should be treated with the appropriate agent, such as a beta-adrenoceptor blocking agent, disopyramide or phenytoin for tachycardia and atropine for bradycardia.

Quinidine, phenytoin, procainamide, and, less often, lignocaine may also induce disorders of cardiac rhythm, as may sympathomimetic agents such as adrenaline, noradrenaline, and isoprenaline. The latter are often used for their chronotropic or inotropic action on the heart, but arrhythmias may occur when they are being used for a non-cardiac indication. Adrenaline, given as a vasoconstrictor with local anaesthetics, may be absorbed in sufficient quantities from vascular tissues to cause ectopic beats. The excessive death rate in young asthmatic patients recorded in the late 1960s has been attributed to the over-use of inhalers containing isoprenaline. Death was often sudden and unexpected, supporting the theory that an arrhythmia due to the sympathomimetic agent may have been the precipitating event in an already hypoxaemic patient. Fluoroalkane gases in the propellant of the inhaler that sensitise the myocardium to the action of the sympathomimetic agent may also have played a part. Halothane may lead to ventricular arrhythmias due to its ability to sensitise the myocardium to catecholamines, either endogenously produced or exogenously administered. Halothane has, in addition, a direct vagal effect, which results in cardiac slowing, and this may be seen during induction of anaesthesia.

Centrally acting drugs with pronounced cardiovascular effects include tricyclic antidepressants, which by virtue of their anticholinergic effect pose problems of cardiac rhythm when taken in overdose. Arrhythmias caused by phenothiazines, such as chlorpromazine, have a similar basis. The management of patients poisoned with overdoses of tricyclics or phenothiazines is difficult, and their prognosis often depends on the ability to prevent or control disorders of cardiac rhythm.

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Depression of cardiac function

Heart failure resulting from administration of beta-adrenoceptor blocking drugs is an example of an exaggerated but otherwise normal drug response. In patients whose myocardial function is preserved only by virtue of a high level of adrenergic drive—that is, after cardiac surgery or in patients in incipient heart failure—administration of beta-blockers can precipitate frank decompensation, accompanied by bradycardia and hypotension. Intravenous administration of beta-blockers to treat a cardiac arrhythmia is not infrequently the precipitating cause. If beta-blockers must be given to patients with incipient failure by either oral or parenteral routes they should be administered very circumspectly and should be covered with digitalis. If heart failure is going to occur the first doses of beta-blockers will usually precipitate this, and thus it is always advisable to start with a low dose for one or two days before building up to an appropriate therapeutic regimen. The bradycardia produced by beta-blockers can be reversed initially by atropine given intravenously to oppose vagal effects. Isoprenaline will antagonise the adverse cardiac effects of beta-blockade on a competitive basis, but large doses may be needed.

Quinidine, procainamide, and lignocaine can all precipitate heart failure and hypotension by depressing myocardial excitability and prolonging the refractory period of cardiac muscle. These effects are dose dependent, and again are usually more evident with intravenously administered drugs, when a relatively larger proportion of the dose is distributed to the heart than when the drugs are given by mouth.

Drug-induced disorders of heart muscle

It is now well established that alcohol may exert a direct toxic effect on heart muscle, independent of the nutritional type of cardiomyopathy (akin to beri-beri) that alcoholics can suffer because of their poor diet. In this "direct" type of alcoholic cardiomyopathy the previous diet may have been quite adequate and replacement of thiamine is without effect. These patients present in heart failure with or without cardiac arrhythmias, and although conventional measures of treating failure at first meet with some success, the overall course is often progressive and downhill. Withdrawal of alcohol (even when possible) is no guarantee of a good outcome. Apparent "epidemics" of heart failure in beer drinkers in the United States were traced to the addition of cobalt to beer to produce a better "head." The death rate from heart failure in these outbreaks was high, but on withdrawal of the cobalt from beer no new cases were seen.

Cardiomyopathy is a well-recorded toxic sign of the antineoplastic agents, daunorubicin and its structural analogue, doxorubicin (Adriamycin). These effects are cumulative dose dependent; the drugs are taken up by the myocardial cells, and at necropsy a striking decrease in the number of cardiac cells can be seen together with degeneration of those remaining. Monitoring of the electrocardiogram and systolic time interval are probably the earliest predictors of toxicity, although awareness by the doctor that these drugs can cause heart failure is the best safeguard.

Experimental animal studies have shown that infusion of catecholamines at high doses can induce areas of myocardial necrosis and focal degeneration—a similar picture is occasionally seen in patients with pheochromocytoma. These changes appear unlikely to occur with therapeutic doses of sympathomimetic agents, but they can be important in overdosage. Post-mortem changes of myofibrillary degeneration have been seen in patients given long-term high-dose phenothiazine treatment. The basis of this is uncertain, but it has been speculatively associated with the ability of phenothiazines to block catecholamine tissue uptake thus leading to high circulatory catecholamine concentrations.

Cardiomyopathy has also been occasionally found after lithium treatment, and this may become more of a problem as its use

increases. More frequent are the abnormalities of cardiac function caused by emetine, used to treat amoebiasis. ECG changes such as T-wave inversion are extremely common, and it is now recommended that everyone given emetine is kept in bed during treatment, and for a few days after. Experimental animal work suggests that these cardiac effects of emetine are caused by its ability to inhibit cardiac protein biosynthesis.

Drugs causing myocardial ischaemia

Coronary artery disease is relatively infrequent in young women, and is at least six times more common in men between 30 and 54 than in women of the same age. Studies such as those carried out by the Royal College of General Practitioners have clearly indicted contraceptive steroids as a precipitating factor in myocardial ischaemia. The incidence of coronary artery and cerebrovascular disease is higher in pill users than those using other methods of contraception, and this is compounded by other factors, such as increasing age, smoking, obesity, and hypertension. The importance of increases in clotting factor concentrations induced by contraceptive steroids as a cause of vascular disease is uncertain, and other changes such as those in blood pressure and plasma lipids must also contribute.

Much effort has gone into examining the association between excessive coffee drinking and myocardial ischaemia; but on current available evidence a causal relation is hard to sustain.

Drug-induced hypertension

Most drugs that cause a chronic rise in blood pressure do so by causing retention of salt and water. Commonest examples are corticosteroids, contraceptive steroids, carbenoxolone, and phenylbutazone. Corticosteroids such as prednisone vary in their sodium retaining ability in patients, and this is paralleled by the variability in the levels of blood pressure in patients with Cushing's syndrome, but death from malignant hypertension has resulted from prolonged corticosteroid treatment. The precise pharmacological basis of contraceptive steroid-induced hypertension is uncertain, but it is now accepted that they cause an average increase of some 4 mm Hg systolic and 2 mm Hg diastolic blood pressure a year. Obviously in some patients the increase is greater, and again, cases of contraceptive-induced malignant hypertension have been reported. Withdrawal of contraceptive steroids does not invariably result in a fall in blood pressure, and, moreover, when the pressure does fall, this may take several months.

Acute rises in blood pressure can be precipitated by interactions between tricyclic antidepressants and the adrenergic neurone-blocking drugs, guanethidine, bethanidine, and debrisoquine. The basis for this interaction depends on the property of the antidepressants to block the uptake of the hypotensive agent into the nerve ending, their site of action. Tricyclics also block the antihypertensive effect of clonidine, but not of α -methyldopa. A similar explanation can be given for the effect of proprietary cough and cold cures containing the indirectly acting amine phenylpropanolamine in reversing the antihypertensive effect of adrenergic neurone-blocking drugs. Better known, perhaps, is the potential of these cold cures to interact adversely with monoamine oxidase inhibitors, as do tyramine-containing foods and monoamine oxidase inhibitors. Sudden interruption of clonidine treatment can precipitate a considerable rise in blood pressure, and this can be accompanied by other manifestations of sympathetic overactivity such as tremor and tachycardia. These effects are exaggerated if the patient is taking a beta-adrenoceptor blocking drug that prevents only the beta (vasodilator) sympathetic response, leaving an unopposed alpha (vasoconstrictor) effect of the excess catecholamines. The remedy for the clonidine withdrawal syndrome is either rapid reintroduction of clonidine itself or administration of an alpha-adrenoceptor blocking agent, such as phentolamine.

Dangerous rises in blood pressure may also occur when patients are given vasopressor agents, such as noradrenaline and angiotensin, systematically. If noradrenaline were given to patients on tricyclic antidepressants an excessive rise in pressure might occur by virtue of the inhibition of neuronal uptake of the catecholamine. The response to noradrenaline is also exaggerated if the patient is on a drug such as guanethidine or reserpine, and this is caused by denervation hypersensitivity. Dopamine, a valuable agent in treating shock, increases renal blood flow and stimulates cardiac output in moderate doses. High doses can stimulate alpha-adrenoceptors and raise blood pressure considerably and may, incidentally, produce cardiac arrhythmias. Blood pressure must be monitored carefully when any vasopressor agent is being given.

Drug-induced hypotension

Hypotensive agents aside, several other unrelated drugs may lower blood pressure as an undesired effect. Among the best recorded are the phenothiazines, by virtue of their alpha-adrenoceptor blocking effect. This is especially important when this group of drugs are given with antihypertensive agents, and usually has a postural element. Many central depressant drugs will cause an unpredictable and unwanted fall in blood pressure, again often of a postural nature, and this may be more evident in the elderly.

Peripheral arterial spasm

Peripheral arterial spasm manifesting as Raynaud's phenomenon and occasionally progressing to gangrene has been

seen in patients taking ergot-containing preparations to excess for migraine. Arterial spasm and occlusion also may occur when intravenous barbiturates or intravenous diazepam are injected intra-arterially in error.

Thrombophlebitis and venous thrombosis

Local vein damage can occur as a result of any intravenous procedure—for instance, venepuncture or insertion of catheters—irrespective of any drug administered. Drugs most often implicated, however, are the antibiotics, amphotericin B and vancomycin, high-concentration sugar solutions, and, less often, diazepam. Considering the widespread use of intravenous contrast media and intravenous barbiturates, the overall risk of venous complications with them appears relatively small.

A major cause for concern is venous thrombosis and thromboembolism with contraceptive steroids. The incidence of venous thrombosis is up to six times greater in women on oral contraceptives, but with the increasing popularity of low-oestrogen-dose preparations the magnitude of this risk should decrease. Patients taking high doses of conjugated oestrogens also have an increased incidence of venous thrombosis, but when used in doses conventionally given for treating menopausal symptoms the risk is apparently not increased compared to a control population.

Further reading

Davies, D M, ed, *Textbook of Adverse Drug Reactions*. London, Oxford University Press, 1976.
Meyler's *Side Effects of Drugs*, ed M N G Dukes, vol 8. Amsterdam, Excerpta Medica, 1976.

Letter from . . . Chicago

Healing by touching

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In 1885 Daniel David ("DD") Palmer pushed a bump on a deaf janitor's neck and promptly restored his hearing—whereupon this Toronto-born former Illinois beekeeper gave up the arts of phrenology and mesmerism, and smashing up his magnetic mirror henceforth applied himself to the science of laying hands on people's spines and adjusting them "without the use of drugs, medicine, or instruments."¹⁻³ Having thus discovered the chiropractic principle of restoring nature's innate life-giving force's ability to flow down the spinal canal ("by relieving any impingement on the delicate nerve fibres"), he became the founder of a discipline that was to endure through the next century. Today some 18 000 chiropractors are

licensed in the United States,⁴ and all 50 States recognise the descendants of the disciples of the man with the "keen mind that fully grasped the scientific principle and the courageous discoverer and humanitarian who—as a man of destiny—gave to the world this priceless gift of health."⁵

The early days of the new cult, however, were inauspicious. In 1905 the founder went to jail rather than pay a \$500 fine for practising medicine without a licence.² Yet by the time of his death in 1913 the science of restoring the free flow of nature's innate intelligence had become fairly well established, owing mainly to the efforts of his son, Bartlett Joshua ("BJ") Palmer, the bearded man who boasted that no razor had ever crossed his chin.² In 1895 the Palmers had established their College of Chiropractic in Davenport, Iowa, "after years of intensive study and research in developing the scientific premise upon which the profession of chiropractic is founded."⁵ Later, after a series of arguments between the two Palmers, the son attempted to run over the father with the school car, and henceforth BJ remained the sole dean of the school until his death in 1961 at the age of 79.¹⁻³

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