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Problems with Digoxin

Radioimmunoassay[1] of digoxin in plasma has shown that the usual steady-state plasma level for therapeutic effect[2 3] is between 1·0 and 2·0 ng/ml. The relation between plasma level and therapeutic effect is not consistent, however, and clinical judgement is still relevant, because of the effect of other changes in the environment of the myocardial cell. The plasma potassium concentration and thyroid status both have important effects on digitalis action, and there are possibly also variations in the relationship between plasma and myocardial cell concentrations of digoxin.[4] The difficulty in predicting an appropriate dose from body weight and indices of renal function[5] suggests that some other individual variable of patient response may be important.

Some problems in the management of digoxin therapy were highlighted in a recent painstaking study from Belfast[6] of the plasma digoxin concentrations in patients receiving maintenance digoxin treatment at the time of emergency admission to hospital. Thirteen of the 101 patients studied were toxic, as judged by the presence of nausea and vomiting or specific rhythm disturbances which resolved when digoxin was stopped. This suggests that toxicity is just as common in outpatients on regular digoxin therapy as it is in patients in the hospital ward.

The mean plasma digoxin level was higher in the toxic group than in the rest, but there was much scatter and the difference was not significant; there was however no difference in the average daily dose, age of the patients, incidence of renal failure, or plasma potassium level. Twenty-five additional patients had plasma levels above 2·0 ng/ml, indicating that there is a large group of potentially toxic patients who did not show evidence of toxicity on admission to hospital but who would be at risk unless further treatment were very cautious.

The high plasma levels in these patients were probably due to the use of very easily absorbed digoxin preparations. Fortunately many patients discontinue digoxin treatment when unwell, either spontaneously or under instruction from their physicians, and this probably avoids some episodes of toxicity. Serious problems arise with obsessional patients who insist on continuing treatment in spite of nausea or other toxic effects and with physicians who give antiemetic drugs or parenteral digoxin in these circumstances.

One third of the patients had plasma digoxin levels of 0·8 ng/ml or less; it seems likely that their treatment was ineffective, but this could not be attributed to failure to take the tablets. In the one third of the patients identified as taking tablets irregularly the plasma levels were not any lower than average, suggesting that some other mechanism is responsible for the low plasma levels. The use of poorly absorbed preparations of digoxin[9] seems a likely explanation. Two patients included in the study denied taking digoxin but had raised plasma levels on admission; one of them, with cor pulmonale, subsequently died after oral digitalizing doses which eventually produced a level of over 4 ng/ml.

In patients with atrial fibrillation the slowing of the ventricular rate by the effect of the drug on the atrioventricular node is a useful guide to the adequacy of therapy. Some confusion has been created by a report[3] that some patients with good control as judged by rates of 60 to 85/minute had plasma levels generally considered ineffective—less than 0·8 ng/ml. Presumably these patients had some intrinsic disease of the conducting system; there are patients with atrial fibrillation who have a slow ventricular rate even without treatment and do not need digitalis. In other patients a relatively rapid rate persists in spite of apparently satisfactory treatment because of associated factors such as persistent heart failure or thyrotoxicosis, but in general the ventricular rate remains a useful guide to therapy in atrial fibrillation. A rapid irregular rhythm from supraventricular tachycardia with block due to digitalis toxicity may be overlooked unless the electrocardiographs are studied carefully.

In those with sinus rhythm the situation is quite different. The slight slowing of the heart rate produced by digitalis is generally obscured by other effects on the sinus node, and the progressive slowing seen in atrial fibrillation is no longer a guide to therapy. Sometimes there may seem to be problems in the adjustment of digoxin treatment being given for an inotropic effect in patients with congestive heart failure in sinus rhythm. In fact the undoubted effect of digitalis in increasing the force of contraction of the heart is quantitatively slight and hard to demonstrate on continued treatment;[10] indeed persistent heart failure has been described as a toxic effect of digitalis treatment,[11] and use of digoxin in the management of congestive cardiac failure in patients in normal sinus rhythm has justly been termed[12] a "clinical nemesis."

A further difficulty arises from the concept of the "full digitalising dose." Though a loading dose is needed to produce an effect quickly, the need to produce a maximal effect must

be based on the hypothesis that doses near to the toxic level will carry dramatic benefit that cannot be obtained with a lower loading dose—or more gradually on conventional maintenance doses of digoxin, which achieve the same effect in a few days.[13] Control of emergency situations such as pulmonary oedema can usually be achieved by diuretic therapy and artificial ventilation if necessary; the added benefit of digitalis treatment is unlikely to be dramatic; attempts to obtain a maximal effect of digitalis treatment are likely to lead to toxicity and should be avoided. To give a "full digitalising dose" to a patient with heart failure in sinus rhythm without detailed consideration of all the problems is a recipe for disaster. The therapeutic margin is very narrow: indeed it has been argued that if digoxin were to be introduced as a new drug today it would be regarded as too toxic for clinical use.

[1] Smith, T. W., Butler, V. P., and Haber, E., *New England Journal of Medicine*, 1969, **281**, 1212.
[2] Smith, T. W., and Haber, E., *Journal of Clinical Investigation*, 1970, **49**, 2377.
[3] Chamberlain, D. A., *et al.*, *British Medical Journal*, 1970, **3**, 429.
[4] Coltart, J., Howard, M., and Chamberlain, D., *British Medical Journal*, 1972, **2**, 318.
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[6] Carruthers, S. G., Kelly, J. G., and McDevitt, D. G., *British Heart Journal*, 1974, **36**, 707.
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[9] Shaw, T. R. D., Howard, M. R., and Hamer, J., *Lancet*, 1972, **2**, 303.
[10] Davidson, C., and Gibson, D., *British Heart Journal*, 1973, **35**, 970.
[11] Gouley, B. A., and Scloff, L., *American Heart Journal*, 1938, **16**, 561.
[12] Knoebel, S. B., in *Digitalis*, ed. C. Fisch and B. Surawicz, p. 121. 1969.
[13] Marcus, F. J., *et al.*, *Circulation*, 1968, **34**, 865.

Black Eyes and Blow-out Fractures

Black eyes are common enough after fights, sports injuries, and accidents, but there is no really effective treatment—the time-honoured beefsteak is both expensive and useless and most of the drugs said to reduce haematomas are not of convincing value.

The important clinical problem is whether a blow-out fracture of the orbit is present. The eye is protected by the bones of the orbit. Blunt trauma, such as from a fist or a ball, tends to force the eye back into the orbit and the hydraulic force may cause the bones to give way in the thinnest place, which is usually in the floor of the orbit. Generally the bones of the orbital margin are intact. Sometimes when the floor is fractured orbital fat and the inferior ocular muscles may herniate through and become incarcerated; the patient will then experience double vision, unless his eye is occluded by the bruised and swollen lid. The double vision will be most marked on attempted vertical gaze. Diplopia may occur as a result of an orbital haematoma without any associated fracture, but this symptom should always lead one to suspect bone damage. The other features of a blow-out fracture include vertical displacement of the eye (easy to measure by using a straight edge and comparing the levels of the corneal margin between the two eyes) and some degree of enophthalmos owing to the reduction of the orbital contents. However, this may be difficult to gauge if the bruising is extensive. The presence of orbital emphysema is not diagnostic of a blow-out fracture but merely suggests that the neighbouring sinuses have been injured. The infraorbital nerve, which supplies the sensory innervation for the lower lid and upper part of the cheek, travels through a bony tunnel in the floor of the orbit. In a blow-out fracture this nerve is often injured, producing numbness in this region. There are, then, no clinical features which guarantee the diagnosis of a blow-out fracture, but the general clinical picture and in particular the presence of diplopia should alert one to the possibility.

Standard skull *x*-rays frequently fail to show the fracture, so if the condition is suspected it is wise to seek advice from the radiologist. Both anterior-posterior and occupito-mental views may be required, as well as the use of tomography. Suggestive signs include opacification of either the maxillary or ethmoid sinuses on the affected side. The herniation of the orbital contents may sometimes be seen in what is known as the "hanging drop" pattern, and in other cases discontinuity of the orbital floor can be clearly shown.

If a blow-out fracture is part of a serious injury to the skull, then its treatment should take a secondary place in the management of the patient's general condition. If the patient is fit, however, treatment should be undertaken urgently. It is not the fracture itself which is important but the fact that the inferior ocular muscles are affected, for if these are not freed within a few days of the injury permanent diplopia may result. The orbital floor represents a demarcation zone between ophthalmologists and E.N.T. surgeons, both of whom may claim expertise in this area—but in fact the treatment is probably best conducted by faciomaxillary surgeons used to handling large numbers of traumatic cases.[1] Before surgery is undertaken it is wise to perform a forced duction test under anaesthesia to be sure that the muscles are trapped. The muscles can be freed either by an approach along the orbital floor or from below through the maxillary sinus. In some instances all that is required is the freeing of the muscles and elevation of the bone, while in others the defect may need to be covered with a piece of silicone sheeting.

[1] Murphy, A. G., *Journal of the Royal Army Medical Corps*, 1974, **120**, 40.

Alcohol and the Small Bowel

Chronic alcoholics are prone to suffer from a variety of gastrointestinal disorders, many of which are well known and have been widely studied—gastritis, the Mallory-Weiss syndrome, pancreatitis, various forms of liver disease, and mucous colitis. They also suffer an increased incidence of gallstones and duodenal ulceration, though opinions differ on the effect of alcohol on acid secretion by the stomach. Symptoms such as anorexia, vomiting, and abdominal discomfort are common, and the frequency of diarrhoea, which may sometimes amount to frank steatorrhoea, suggests that alcohol may interfere with small-bowel function. Various degrees of malabsorption of fat, nitrogen, vitamin B_{12}, and folate can in fact be shown in some alcoholics without obvious liver or pancreatic disease, and defective D-xylose excretion is frequent.[1-4] Though one or more indices of absorption can be found to be affected in most patients—83% in one series[2]—they do not necessarily parallel each other, and it is likely that several mechanisms are responsible.

One possibility, in view of the abnormal D-xylose tests, is that alcohol might damage the jejunum; but jejunal biopsies have generally been reported to be normal[3 4] though megaloblastosis has been noted in the epithelial cells of crypts and