Damage to the Intrinsic Cardiac Neurones by Rubidomycin (Daunorubicin)

BARBARA SMITH

From St. Bartholomew's Hospital, London E.C.1

Rubidomycin is an antineoplastic antibiotic which was produced in France from *Streptomyces caeruleo-rubidus*. It is used mainly in acute myeloblastic leukaemia, in which it is as successful in inducing remissions as any other therapy at present available (Malpas and Scott, 1968). It is, however, very toxic, and the administration may result in marrow aplasia or myocardial failure.

MATERIAL

The material used was taken at necropsy from 7 patients with acute leukaemia who had been treated with rubidomycin (Table). In addition to tissue for routine post-mortem investigation, four to six posterior root ganglia, a sympathetic chain, a portion of sigmoid colon, and the whole heart were taken. The ganglia were examined in paraffin sections and stained with haematoxylin and eosin, methyl green pyronin, and Holmes-luxol-fast blue. The colon was cut in frozen sections parallel to the myenteric plexus (Smith, 1967), and stained by Schofield's method. Blocks were taken from atria and ventricles of the heart for paraffin sections, and from the posterior wall of the right atrium for silver impregnation of frozen sections.

TABLE

Case No.	Sex	Age (yr.)	Diagnosis	Electro-cardiogram	Dose of rubidomycin (mg.)
1	M	52	Acute myeloid leukaemia	Normal	480
2	M	49	" "	Abnormal	560
3	M	42	" "	Abnormal	236
4	F	56	" "	Abnormal	380
5	F	65	" "	Abnormal	480
6	M	40	" "	Abnormal	450
7	M	55	Acute lymphatic leukaemia	Abnormal	160

RESULTS

Posterior Root Ganglia. The neurones showed a succession of changes. The earliest appeared to be

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FIG. 1.—Case 2. A posterior root ganglion. The ribosomes have clumped together to form large masses. (Haematoxylin and eosin. $\times 185$.)

FIG. 2.—Case 1. A posterior root ganglion. Four adjacent cells are dead and engulfed by amphicytes. (Haematoxylin and eosin. $\times 185$.)

FIG. 3.—Case 5. A cardiac ganglion. Several cells are dead and engulfed by amphicytes. (Haematoxylin and eosin. $\times 93$.)

FIG. 4.—A cardiac ganglion from a patient dying from an astrocytoma. The cells are small and have a number of fine processes. (Schofield. $\times 93$.)

FIG. 5.—Case 6. A small cardiac ganglion showing two cells, one of which is certainly dead; the other is enlarged and shows a rounded swelling on one process. (Schofield. $\times 93$.)

a purplish staining of the nucleus with crenation of the nuclear membrane. The nucleolus became relatively large in relation to the nucleus so that it appeared to occupy the greater part of it. The nucleolar membrane was lost, and the two structures merged into a shrunken, misshapen mass. The cytoplasm was usually devoid of ribosomes, but this is common in post-mortem material. In two cases the ribosomes appeared to have clumped together to produce large pyroninophilic structures (Fig. 1). There was proliferation of amphicytes going on to acute neuronophagia (Fig. 2) and later to residual corpuscles. The latter were not frequent, probably because of the short duration of the damage.

Sympathetic Chain. In some cells there was a similar nuclear change to that seen in the posterior root ganglia, but there was very little evidence of cell destruction.

Myenteric Plexus. The changes were not very striking. There were a few neurones with very swollen and abnormal processes and an occasional retraction ball.

Heart. Paraffin sections of the ventricles showed no abnormality. Sections of the atria showed an increase in fibrous tissue and some muscle fibres were pale and vacuolated. The neurones were very variable. Some were within normal limits, and some had lost their nuclear membrane, the whole cell staining a purplish colour with haematoxylin and eosin. Many of these cells were grossly shrunken. Proliferation of amphicytes was apparent, but only Cases 1 and 5 showed neuronophagia (Fig. 3). The silver preparations showed more striking abnormalities. The cells appeared pale and rounded, the processes were swollen and misshapen, and some were enormously enlarged with no processes at all (Fig. 4 and 5). The amphicyte proliferation was more apparent on the thicker sections. The extrinsic nerves, both sympathetic and parasympathetic, were normal.

DISCUSSION

Abnormalities of posterior root ganglia are difficult to assess. All the changes described in these cases can be seen occasionally in routine necropsies, particularly in patients dying from malignant disease. In any patient with a debilitating illness the normal loss of neurones due to ageing appears to be increased. However, the striking feature in these ganglia was the extent of the damage. In 4

cases out of 7 very few normal nuclei could be found in the sections, and the number of disintegrating cells was high. The unusual feature in this group of cases is the damage to the intrinsic cardiac innervation which is not seen to any extent in patients with leukaemia treated with other drugs. In similar conditions treated with the vinca alkaloids the brunt of the damage falls on the myenteric plexus (Smith, 1968), but this structure appears to be relatively unaffected by rubidomycin. This is probably not a reflection of any difference in the neurones but of the way the drugs are handled by the body and the tissues in which they achieve their maximum concentration. There is good clinical evidence that rubidomycin is concentrated in the heart. Abnormalities of the electrocardiogram during treatment are common, being mainly inverted T waves (Malpas and Scott, 1968), and were seen in 6 of the above cases. A number of patients have died from heart failure (Macrez *et al.*, 1967). Ripault, Weil, and Jacquillat (1967) reported histological abnormalities in the myocardium and mural thrombus in the ventricle in a child of 10 who had received the drug. The patients reported here, who had abnormal electrocardiograms while receiving the drug, all recovered, and their last electrocardiogram was normal, except for the sinus tachycardia which was always present. No patient died in heart failure. Ventricular abnormalities would therefore not be expected histologically. The significance of the changes in the atrial muscle are somewhat doubtful, but the increased fibrosis, which was quite definite and occurred in every case, might indicate some previous necrosis.

Much experimental work has been done on cardiac vagotomy and sympathectomy, but nothing is known of the physiological effects of destroying the intrinsic cholinergic innervation, either on the myocardium or the coronary vessels. The sympathetic supply is intact and virtually unopposed, and there are no protective cardiac reflexes. The patients have a conspicuous sinus tachycardia, and it is possible that the myocardium is being driven too hard for its coronary blood flow. This may contribute to the myocardial insufficiency.

It is interesting that antimetabolic drugs which are given specifically to damage rapidly dividing cells should have so much effect on neurones which do not divide at all. Rubidomycin is identical with

daunomycin* (Tong, Lim, and Goodman, 1967). Its antimetabolic activity is related to its effect on nucleic acid metabolism. It binds to the DNA molecule in a similar manner to actinomycin and inhibits the DNA-dependent RNA polymerase (Di Marco, 1967). It thus stops RNA synthesis as does actinomycin, but unlike this drug it also inhibits DNA synthesis to some extent. Neurones contain large quantities of RNA and are dependent on it for normal functioning. It is possible that if RNA synthesis in neurones is stopped, cell damage may occur. The early changes in the nucleolus are also in favour of this suggestion. Interference with RNA metabolism is a feature of many antineoplastic antibiotics, and some permanent damage to the peripheral nervous system seems likely if these patients survive long enough.

SUMMARY

Damage to the peripheral neurones is produced by the antimetabolic drug, rubidomycin. The predominant effect on cardiac neurones may be related to the fact that the drug is concentrated in the heart. Drugs which disrupt RNA synthesis are likely to produce neuronal damage if they reach these cells in sufficient concentration.

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* The terms rubidomycin and daunomycin have now been discontinued, and the name daunorubicin is used for both drugs.