sample of 2,6-dichlorophenylguanidine (Fig. 1) with molecular ions at *m/e* 203, 205, 207 (relative intensities 9:6:1) and fragment ions at *m/e* 161, 163, 165 (relative intensities 9:6:1). This pattern of three ions at 2 mass unit intervals with relative intensities 9:6:1 is characteristic of compounds containing two chlorine atoms. The authentic 2,6-dichlorophenylguanidine which was prepared by ammonolysis of 2,6-dichlorophenylimidocarbonyl chloride in boiling dioxan (Appleby, private communication) had identical chromatographic properties to those of the metabolite. Although quantitation was not possible, the intensity of fluorescence quenching on t.l.c. plates viewed under ultraviolet light suggests that 2,6-dichlorophenylguanidine may be a major metabolite of clonidine in dog urine. This compound is known to possess only weak hypotensive activity in the dog and the rat (Jen, van Hoeven & others, 1975).

This is believed to be the first observation of the metabolism of a 2-aminoimidazoline compound by a net bis-*N*-dealkylation although a similar type of ring cleavage has been reported for the piperazine ring in the drug perazine (Breyer, Krauss & Jochims, 1972; Gaertner & Breyer, 1972).

The substance from rat urine with the R_F value 0·82 was identified as unchanged clonidine by its behaviour on t.l.c. and by mass spectrometry of the material isolated from t.l.c.

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On the biological half-life of amitriptyline

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Little has so far been published about the biological half-life of amitriptyline. In 1971, Braithwaite & Widdop obtained figures of 41 and 45 h with two volunteers, in whom the biological half-life was determined from the declining plasma concentration curves after cessation of dosing to steady state (amitriptyline 3×50 mg day^{-1}). Hucker, Stauffer & others (1975) recorded an apparent plasma half-life of approximately 8 h. But this was obtained from the period 9–12 h after administration of a sustained release formulation of amitriptyline (Hucker, personal communication), a period which is not purely elimination phase (β-phase). Since part of the decline in plasma concentration in this period is due to distribution from plasma into the tissues this figure cannot be considered an estimate of the biological half-life of amitriptyline.

Based on a study with once a day administration of amitriptyline to eight patients we have been able to estimate the biological half-life of amitriptyline from data from

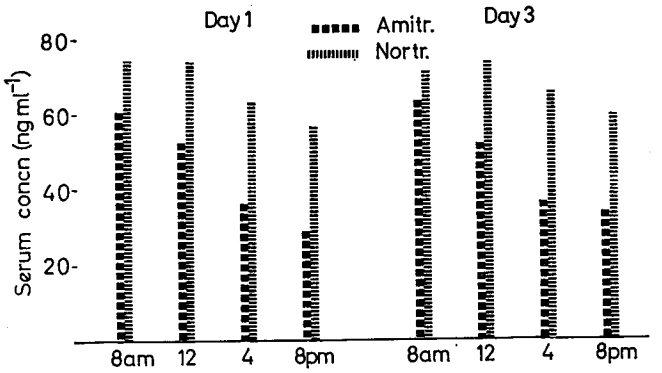

FIG. 1. Serum concentrations of amitriptyline and nortriptyline in one of the eight patients.

the elimination phase, 12 to 24 h after administration. Each patient received a single daily dose (100 mg) of a sustained release preparation of amitriptyline (Saroten Retard, Lentizol) at 8 pm. After two weeks of treatment four blood samples were drawn on each of two days (1 and 3) separated by one day, on which no blood samples were drawn but the drug was taken. The sampling times were 8 am, 12, 4 and 8 pm, i.e. 12, 16, 20 and 24 h after the drug had been given. Serum was obtained from the blood samples by centrifugation and stored frozen until analysed. The serum concentrations of amitriptyline and its metabolite, nortriptyline, were determined according to Jørgensen (1975).

Serum concentrations obtained for amitriptyline and nortriptyline in one patient are shown in Fig. 1. It appears that the serum concentration of amitriptyline steadily decreases while that of nortriptyline is relatively constant. A regression analysis was made using the log concentration—time data for amitriptyline. The linearity of the regression line was tested (90% level) and the biological half-life calculated. The results from the eight patients are in Table 1. The regression lines show linearity (i.e. the serum concentration curves decline monoexponentially) in all but four cases indicating that the blood samples originate from the elimination phase (β-phase). The non-linearity seen in four cases [II, day 1 (10·7) and 3 (12·3); IV, day 1 (9·4); and VIII, day 3 (14·8)] is most likely not due to influence from drug absorption and distribution, since only a very low value at one of the sampling times (at 4 pm in three cases and at 12 pm in one case) spoils the linearity.

From Table 1 the range of the biological half-lives is 9·0 to 25·3 h. The mean half-life is 15·1 (s.d. 4·8) (the non-linear cases excluded). In four of the five patients

Table 1. *Linearity of the regression lines and the calculated biological half-lives of amitriptyline.*

Patients	Body weight (kg)	Sex	Age (years)	Day 1 Linearity	Day 1 Biological half-life (h)	Day 3 Linearity	Day 3 Biological half-life (h)
I	68	M	49	+	11·7	+	12·0
II	65	M	49	—	n.m.	—	n.m.
III	75	M	40	+	10·3	+	25·3
IV	75	M	53	—	n.m.	+	9·0
V	80	F	41	+	21·3	+	15·9
VI	71	F	47	+	13·0	+	13·0
VII	77	M	49	+	17·3	+	19·3
VIII	70	M	52	+	13·6	—	n.m.

n.m. = not monoexponential.

(I, V, VI and VII) where linearity of the regression lines was seen both on day 1 and day 3 a good accordance was seen between the half-lives calculated on the two days. Also in the patients with non linearity on one or both days (II, IV, and VIII) the biological half-lives are in agreement with each other. Only in one patient (III) was a big difference seen between the biological half-lives on the two days. Since III was the only patient in the group who received other drugs during the study (diazepam, nitrazepam and lithium carbonate) the difference is possibly due to a varying influence from these drugs on the elimination and/or metabolism of amitriptyline. None of the three drugs or their metabolites interfere with the determination of amitriptyline and nortriptyline. The calculated mean biological half-life of 15·1 h differs widely from that reported by Braithwaite & Widdop (1971). This may be because they used healthy volunteers, while we used patients. However, data (Jørgensen & Hansen, to be published) from an infusion study with four volunteers treated according to a two compartment open model give elimination half-lives in the range 15·5–19·5 h.

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On the direct or indirect influence of apomorphine on central serotonin neurons

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Apomorphine, regarded as a drug stimulating central dopaminergic structures (Andén, Rubenson & others, 1967; Ernst, 1967), increased the concentration of 5-hydroxytryptamine (5-HT) and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in whole rat brain (Grabowska, Antkiewicz & others, 1973; Scheel-Krüger & Hasselager, 1974) as well as in separate brain structures (Grabowska, & others, 1973), particularly in the mesencephalon region. Histochemical fluorescence analysis demonstrated marked increase of 5-HT fluorescence in the region of nucleus raphé dorsalis of rat under the influence of apomorphine (Śmiałowska, 1975).

The experiments presented here were performed to find out if apomorphine affected the 5-HT rich area of the mesencephalon directly or through descending pathway originating from dopaminergic structures of the forebrain.

Male Wistar rats (180–200 g) were treated with atropine (0·1 mg kg^{-1}, i.p. 0·5 h before operation) and were placed in a head holder when slightly anaesthetized with diethyl ether. A dorsal-ventral cut was made through the occipital cortex and the frontal parts of the superior corpora quadrigemina and the nucleus interpeduncularis. The transection totally separated the mesencephalon and the diencephalon. The raphé region in the mesencephalon with the 5-HT containing cell bodies was left intact caudally to the lesion.

Fourteen to 16 h after transection the concentration of 5-HT and 5-HIAA in the whole mesencephalon was simultaneously determined using the methods of Maickel, Cox & others (1968) and Miller, Cox & others (1970) respectively. Apomorphine was administered subcutaneously 45 min before decapitation.

The intensity of 5-HT fluorescence in the cell bodies of the nucleus raphé dorsalis area was evaluated according to Falck, Hillarp & others (1962) 2–4 h after the mesencephalic-diencephalic transection. Apomorphine was injected 30 min earlier. This