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Antispasmodic action of quaternary compounds administered orally

Hyoscine *N*-butylbromide, a spasmolytic quaternary ammonium compound, has been reported to be less effective after oral than parenteral administration (Guignard, Herxheimer & Greenwood, 1968; Herxheimer & Haefeli, 1966). But when it was administered enterally to anaesthetized animals, an appreciable spasmolytic effect was found by Pennefather, McCulloch & Rand (1968) and Pomeroy & Rand (1969). These differences may be related to differences in species, in drug administration routes, and to such factors as anaesthesia and surgical intervention. We have examined the quaternary antispasmodics, hyoscine *N*-butylbromide and *N*-(2,2-diphenyl-1,3-dioxolanyl-4-methyl)piperidinium methylbromide, in unanaesthetized rabbits to determine whether they are effective after oral administration.

Male rabbits (2·5 to 3·5 kg) were laparotomized under sodium pentobarbitone (35 mg kg^{-1}, i.v.) anaesthesia. A rubber microballoon was implanted into the muscle layer of the pyloric antrum (Fig. 1). At least three days after the implantation, and after being fasted for 24 h, rabbits were used without anaesthesia. The internal pressure of the balloon was adjusted to 5 cm H_2O during muscle relaxation.

The antispasmodics used were hyoscine *N*-butylbromide, atropine sulphate, papaverine hydrochloride, *N*-(2,2-diphenyl-1,3-dioxolanyl-4-methyl)piperidinium methylbromide (Anacoline, Toyamakagaku, Toyama, Japan) and *N*-(2,2-diphenyl-1,3-dioxolanyl-4-methyl)piperidine hydrochloride (tertiary analogue of Anacoline). These drugs were administered into the auricular vein or into the stomach by a feeding tube. Normal saline solution was used as vehicle and all doses of the drugs were given in 1 ml kg^{-1} intravenously or 10 ml kg^{-1} orally. Changes in the internal pressure of the balloon were recorded by a low pressure transducer before and after drug

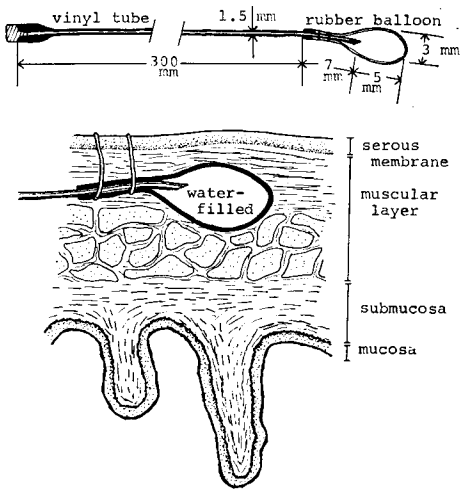

FIG. 1. The rubber microballoon and its site of implantation into the muscular layer of pyloric antrum. The thin vinyl tube connected with the balloon was filled with water and was attached to a low-pressure transducer.

administrations. The duration (min) of the period during which contractile activity was reduced to less than 10% of the average for the 5 min before drug administration was used as an index of antispasmodic activity.

The experiment was repeated five times for each dose of the drug. A four-point assay was employed for the spasmolytic potency ratios. One group of rabbits was used for the experiments with papaverine, atropine and hyoscine *N*-butylbromide and the other group for the experiments with Anacoline and its tertiary analogue.

The dose-response lines for each drug administered intravenously or orally are presented in Fig. 2A, B. The potency ratios of hyoscine *N*-butylbromide and papa-

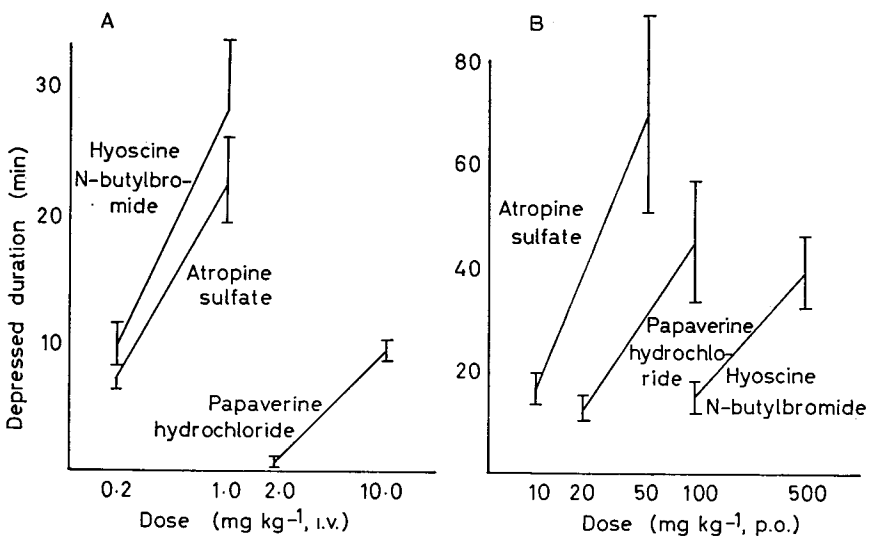

FIG. 2. A. Dose-response lines of atropine, papaverine and hyoscine *N*-butylbromide after intravenous administration. Vertical lines indicate standard errors.

B. Dose-response lines after oral administration of atropine, papaverine and hyoscine *N*-butylbromide.

Table 1. *The spasmolytic potency ratios of papaverine and hyoscine* N-*butylbromide to atropine for both intravenous and oral routes and the oral to intravenous ratios for each drug, and the antispasmolytic potency ratios of* N-(*2,2-diphenyl-1,3-dioxolanyl-4-methyl*)*piperidinium methylbromide* (*Anacoline*) *for both intravenous and oral routes and the oral to intravenous ratio for each drug. The figures in parentheses show the* 95% *fiducial limits.*

	Atropine sulphate	Papaverine hydrochloride	Hyoscine *N*-butylbromide	Anacoline	Tertiary analogue of anacoline
Intravenous	1	0·026 (0·01 ~ 0·04)	1·45 (0·7 ~ 3·5)	1	0·56 (0·26 ~ 1·15)
Oral	1	0·29 (0·06 ~ 0·70)	0·051 (0·01 ~ 0·10)	1	0·34 (0·01 ~ 0·78)
Ratio Oral: i.v.	0·074 (0·02 ~ 0·8)	0·62 (0·1 ~ 2·6)	0·0036 (0·001 ~ 0·01)	0·014 (0·002 ~ 0·023)	0·045 (0·017 ~ 0·06)

verine to atropine and the ratios of the action of the drugs given orally to that of the drugs administered intravenously are shown in Table 1. The order of potency ratios was as follows; intravenous route: hyoscine *N*-butylbromide > atropine > papaverine; oral route: atropine > papaverine > hyoscine *N*-butylbromide; ratio of oral to intravenous: papaverine > atropine > hyoscine *N*-butylbromide. With 1,3-dioxolane derivatives, the oral potency ratio of the tertiary to the quaternary compound was not significantly different from that when these drugs were administered intravenously (Table 1). In other words, the quaternary 1,3-dioxolane derivative was effective after oral administration.

Hyoscine *N*-butylbromide, papaverine and atropine were less effective after oral than after intravenous administration, the differences being greater for hyoscine *N*-butylbromide. These results are consistent with the previous clinical reports (Guignard & others, 1968; Herxheimer & Haefeli, 1966), and with the generally accepted rule that unionized molecules are absorbed without difficulty from the gastrointestinal tracts.

On the other hand, reduction in the spasmolytic activity of the quaternary 1,3-dioxolane (Anacoline) is almost the same as that of its tertiary compound in the unanaesthetized rabbit after oral administration. Therefore the view that reduction in the antispasmodic activity of quaternary drugs administered orally is greater compared with the corresponding tertiary drugs cannot be sustained as a general rule.

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