ABSORPTION STUDIES WITH A SUSTAINED RELEASE TABLET

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The absorption of nitroglycerine, lobeline hydrochloride, radioactive ammonium bromide, creatinine, potassium penicillin V, and dihydromorphinone hydrochloride from sustained release tablets has been investigated in cats and in man. The substances were absorbed more slowly from the sustained release tablets than from conventional tablets. With the sustained release tablet fewer side-effects were seen with dihydromorphinone and a lower utilisation of creatinine and potassium penicillin V was observed. *In vitro* and *in vivo* conformity was good where a comparison could be made.

The principle and *in vitro* control of a sustained-action preparation with the active substance compactly embedded in a porous plastic tablet have been described previously by Sjögren and Fryklöf (1960) and Sjögren (1960). The plastic material, which is insoluble in the digestive fluids, allows only the drug particles at the surface to dissolve. The fluids cannot reach the particles embedded beneath until the surface particles are dissolved. This action progresses successively through the tablet, giving sustained release. The rate of release can be varied over wide limits by modifications in the manufacturing process. The rate of release is relatively unaffected by varying amounts of liquid, mechanical treatment and changes in pH, digestive enzymes, viscosity, surface tension and electrolyte concentration.

Investigations with several substances in this kind of sustained release preparation is now described. Initially tests were made on cats. Later absorption investigations were made in man. In all tests the sustained release tablets were compared with conventional tablets or solutions of the drug or substance being examined. All *in vitro* results were obtained by the method described by Sjögren (1960).

Experiments in Cats

Cats were anaesthetised with chloralose and urethane in doses of 60 and 100 mg./kg. weight respectively. Conventional tablets or sustained release tablets of nitroglycerine and lobeline hydrochloride were introduced directly into the small intestine with 20 ml. of normal saline through a cannula inserted in the duodenum. The doses were chosen so that a strong but not maximum biological effect was obtained. The absorption of the nitroglycerine was inferred from the induced fall in the mean arterial blood pressure, which was continually recorded from one of the femoral arteries. The absorption of the lobeline was estimated from the induced hyperventilation reflex and the respiratory irregularities. The respiratory movements were recorded by pneumatic tubes placed around the lower part of the thorax and connected to a piston recorder.

The mean values and general trends of the experiments with 10 cats are illustrated in Figs. 1 and 2. Nitroglycerine in the sustained release form gave a slower onset and a longer duration of action than when in

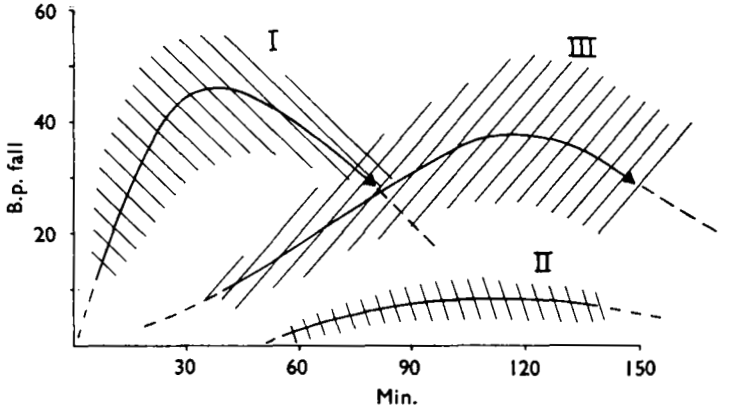

FIG. 1. Effect of nitroglycerine on blood pressure on cats.
I. 3 mg./kg. in conventional tablets
II. 3 mg./kg. in sustained release tablets
III. 10–15 mg./kg. in sustained release tablets.

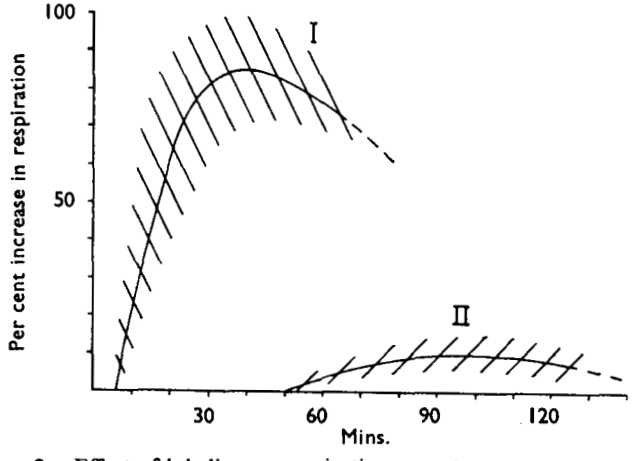

FIG. 2. Effect of lobeline on respiration on cats.
I. 30 mg./kg. lobeline hydrochloride in conventional tablets.
II. 30 mg kg. lobeline hydrochloride in sustained release tablets.

conventional tablets. To reach the same peak response a 3–5 times larger dose was required when administered in the long-acting tablets (Fig. 1). The trials with lobeline gave analogous results (Fig. 2).

EXPERIMENTS IN MAN

Radioactive Ammonium Bromide ^{82}Br

Two groups of four subjects fasted before the experiment and received no food during the first 4 hr. They emptied the bladder immediately

before the experiment and two blood samples were taken to measure the radioactivity of the serum. Blood samples were taken ¼, ½, 1, 1½, 2, 3, 4, 6, 12 and 24 hr. after ingestion of 2 mg. radioactive ammonium bromide (activity 14 mc/g.) as a solution or as sustained release tablets. The blood samples were analysed by measuring the γ-radiation with a Well-crystal and scintillation detector and were compensated for decay and background. Urine samples were taken regularly during the experiment but the amount of radioactive bromide which was excreted in urine was found to be less than 1 per cent of the ingested activity and therefore negligible.

To obtain comparable values between the individuals, the radioactivity in the samples is given as per cent of the maximum value for each person,

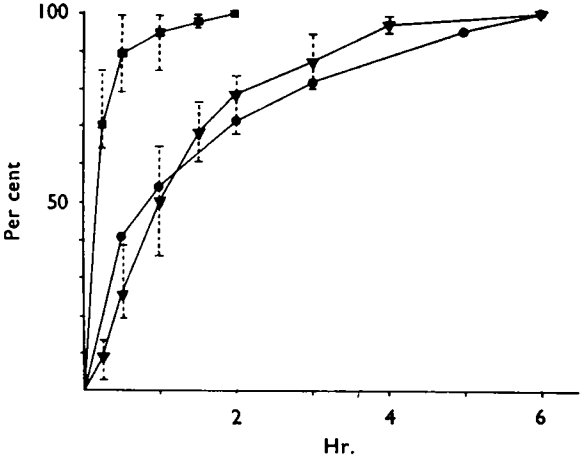

FIG. 3. Release *in vitro* and absorption of radioactive ammonium bromide.
● Amount released *in vitro* from sustained release tablets containing 2 mg. ammonium bromide.
■ Amount absorbed *in vivo* after administration of 2 mg. ammonium bromide in solution (mean value and variation range from 4 persons).
▼ Amount absorbed *in vivo* after administration of 2 mg. ammonium bromide in sustained release tablets (mean value and variation range from 4 persons).

who received either the solution or the sustained release tablets but not both, otherwise for safety it would have been necessary to allow an interval of at least 16 days between the series.

The mean values and ranges from the absorption trials are shown in Fig. 3 together with the *in vitro* release.

Creatinine

Five young healthy males fasted for 12 hr. before the experiment. Blood and urine samples were first taken and then the tablets were given with 300 ml. of water. 20 ml. blood samples were taken after 1, 2, 3, 4½, 6, 7½ and 9 hr. and centrifugated immediately. Urine was collected every 3 hr. A standard meal of two sandwiches and 300 ml. of water was taken after 3, 6 and 9 hr. The subjects were seated during the experiment. Each subject received on the first occasion, 24 placebo

tablets on the second 24 creatinine tablets of 125 mg. and on the third the same number of sustained release tablets of the same strength. Creatinine in the plasma and urine was determined according to a modification of the alkaline picrate method of Owen and others (1954).

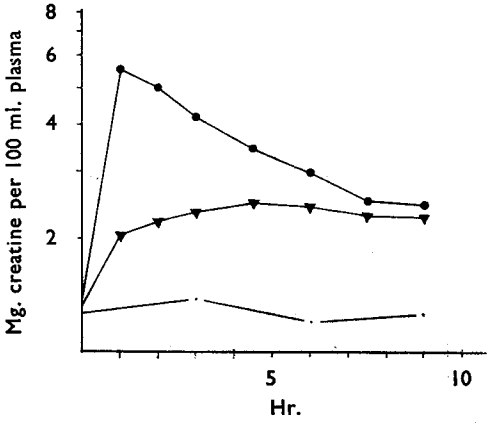

FIG. 4. Creatinine blood concentration (mean values from 5 persons)
● 3 g. creatinine in conventional tablets
▼ 3 g. creatinine in sustained release tablets
· Control

The resulting plasma concentrations are shown in Fig. 4 and the excretion in Table I. The placebo experiments show that the creatinine concentration was, on average, constant and so was the excretion. Conventional tablets showed a rapid absorption. The maximum concentration was reached after 1 hr. and was about 4 mg./100 ml. higher than the

TABLE I

URINE EXCRETION OF CREATININE

	mg./hr. at hr.		
	0–3	3–6	6–9
Placebo	87	87	85
3 g. creatinine in conventional tablets ..	312	276	167
3 g. creatinine in sustained release tablets ..	127	176	112

basic value. The concentration then declined relatively rapidly and, after 9 hr., was about 1 mg./100 ml. above the basic value. The average creatinine excretion during the 9 hr. was 1·48 g. greater than in the placebo trials. The total amount absorbed was about 65 per cent of the ingested amount. The sustained release tablets gave a lower, but more constant, blood concentration of about 1 mg./100 ml. over the basic value from 1 to 9 hr. The excretion of the creatinine during 9 hr. was 0·45 g. greater than in the placebo experiments. The total amount absorbed can be estimated at about 33 per cent.

The sustained release tablets released the creatinine *in vitro* with a relatively constant rate for about 5 hr. (see Table II).

Potassium Penicillin V

The experiment was made on 36 fasting, healthy subjects, each served as his own control, conventional and sustained release tablets containing 500,000 I.U. of penicillin being taken on alternate occasions. A light standard meal was given 4 hr. after taking the antibiotic. Blood samples,

TABLE II

RELEASE *in vitro* FROM SUSTAINED RELEASE TABLETS USED IN THE ABSORPTION TRIALS

Sustained release tablets containing	Per cent released at hr.						
	1	2	3	4	5	6	7
Creatinine 125 mg.	25	45	63	77	90	98	100
Potassium penicillin V 160 mg.	46	90	99	—	—	—	—
Dihydromorphinone hydrochloride 6 mg. ..	48	57	66	74	82	90	96

from the finger tips, were taken immediately before the tablets and then after ½, 1, 2, 3, 4 and 6 hr. The amount of penicillin in the samples was determined by the filter plate technique of Eriksson (1960).

The depot tablets released the penicillin dose in 2 hr. (Table II). Even this slight prolongation of supply gave a clear alteration of the blood concentration curves as shown in Fig. 5.

Dihydromorphinone Hydrochloride

The pain threshold was assessed in 11 untrained fasting subjects (age 23–26 years) initially and 1, 2, 4, 6 and 8 hr. after the ingestion

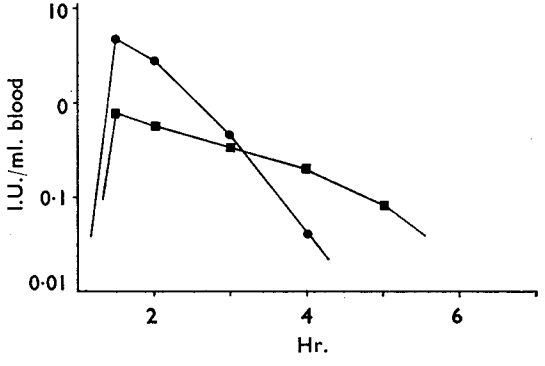

FIG. 5. Blood concentration of penicillin (mean values from 36 persons)
● 500,000 units penicillin V potassium in conventional tablets.
■ 500,000 units penicillin V potassium in sustained release tablets.

of the tablets. Placebo or 6 mg. dihydromorphinone hydrochloride in ordinary or sustained release tablets were given in turn to each subject with at least two days interval between experiments. No food was allowed during the first hr. Subjects were seated comfortably and did not smoke throughout the experiment. The pain threshold was determined by irradiation on the forehead (300 millical./cm.^{2}) with a Hardy-Wolff-Goodell Dolorimeter (Boreus and Sandberg, 1955, 1959).

Measurements were made at six places of the forehead and the mean value calculated. The analgesic effect was reflected in extended reaction time in comparison with the placebo experiments. The statistical calculation of the significance of the results was made as described by Boreus and Sandberg (1959).

Fig. 6 illustrates the results. Both kind of tablets containing dihydromorphinone hydrochloride gave, at all the evaluations from 1–8 hr., a higher pain threshold than placebo. The differences were statistically significant (P = 0·05–0·01). The sustained release tablets gave a higher

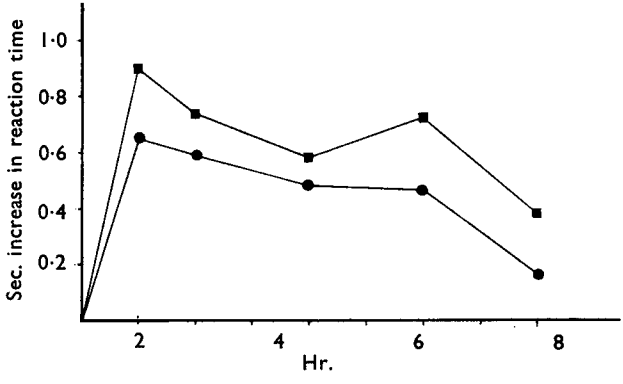

FIG. 6. Analgesic effect of dihydromorphinone hydrochloride expressed as reaction time in excess of the corresonding placebo results (mean values from 11 subjects)
■ 6 mg. in sustained release tablets
● 6 mg. in conventional tablets

pain threshold than the conventional tablets at all the evaluations. The difference was significant. (P = 0·05.)

The *in vitro* release from the sustained release tablets is shown in Table II.

DISCUSSION

Investigations with this type of sustained release tablet containing sodium nitrite have previously been described by Sannerstedt (1960). He found that compared with conventional tablets larger doses were tolerated and a prolonged action could be attained. Two of the compositions investigated released most of the active substance *in vitro* within 4 hr. One released the main part in the first hr. and the other during the third and fourth hr. The first composition gave a rapid blood pressure fall which remained constant through the 4 hr. whereas the other also gave a rapid pressure fall, but did not attain maximum effect until the third hr.

The methods used in the present investigation with the nitroglycerine and lobeline preparations could not give an exact conception of the absorption rate or degree of utilisation, but they did show that the two drugs in the sustained release form had a slower onset of action and that to obtain the peak effect reached with conventional tablets required much larger doses of the sustained release form of the drug. The duration

of action was difficult to evaluate, a quantitative measure of duration was not obtained, but a qualitative difference was seen.

The experiment with radioactive ammonium bromide was intended to show the association between the release of the active substance *in vivo* and *in vitro*. It is known that bromide ions are easily absorbed and slowly eliminated. The measurements of radioactivity confirmed this. Excretion was insignificant compared with the absorption. The sustained release tablets clearly gave a more prolonged absorption than the solution. The absorption rate agreed well with the release rate for the preparation *in vitro*. The range of the results was similar for the solution and the sustained release tablets, which suggests that the release of activity from the tablets was similar from one individual to the other.

Creatinine has the advantage of being easily and accurately determined in blood and urine. It is absorbed quickly, but not completely, and, apparently, is not metabolised but almost entirely excreted in urine. The sustained release administration gave a lower peak and a more even concentration of creatinine in plasma than the conventional administration, which indicates a continual supply of the substance. The poorer absorption from the sustained release tablets may be caused by a decreasing absorbability along the alimentary canal or an effect of greater dilution. Dominguez and Pomerene (1945) found that absorption ceased 2 hr. after oral administration of creatinine in solution.

Penicillin is easy to determine in blood in therapeutic concentrations, but to maintain an even blood concentration is difficult as it is rapidly excreted. Oral penicillin also gives erratic blood levels because of poor absorption and variable inactivation in the gastrointestinal tract. The sustained release tablets gave a lower peak concentration than conventional tablets in all subjects but gave a longer duration only in a third. The results of the experiments show that potassium penicillin V is not suitable for this type of administration. A slower release of the antibiotic from the tablet is suggested by the results, but no definite conclusions can be drawn about the rate of release.

In the experiments with dihydromorphinone hydrochloride the pain threshold was always higher with the sustained release tablets than with conventional tablets. This unexpected result, with a lower grade of efficiency from the conventional tablets even initially, might depend on the side effects of these tablets (nausea and vomiting). There were no side-effects with the sustained release preparation. The results show that sufficient absorption is obtained from the sustained release preparation to prolong the effect of the drug and that with the drug in this form there is a much reduced risk of side-effects.

In the various trials the sustained release preparation gave a lower peak and a more even drug concentration or action, which indicates that the preparation releases the active ingredient continually as suggested by the *in vitro* analyses. The rate of release *in vivo* is difficult to estimate but seems to agree fairly well with the *in vitro* values in the experiments with radioactive bromide as well as in the investigations described by Sannerstedt (1960).

A lower availability from the sustained release tablets was found with creatinine and potassium penicillin V, and that might depend on rapidly decreasing absorption for these substances along the gastrointestinal tract.

The lower peak concentrations obtained suggest a possibility of reducing side-effects for certain drugs as was demonstrated in the case of dihydromorphinone as well as in the investigations by Sannerstedt (1960).

In earlier trials with this skeleton type of sustained release tablet uncertainty prevailed about discomfort that might be caused to the patient by the undissolved plastic skeleton. No discomfort has been reported over the 5 years that this preparation has been tested.

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