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On the disintegration of hard gelatin capsules in fasting volunteers using a profile scanning technique

M. ALPSTEN, C. BOGENTOFT*‡, G. EKENVED*, L. SÖLVELL†, *Department of Radiation Physics, University of Göteborg, Sweden, *AB Hässle, Fack, S-431 20 Mölndal 1, Sweden, †Mölndal Hospital, Box 122, S-431 22 Mölndal, Sweden*

Hard gelatin capsules have become a common and useful oral dosage form for drugs. Several studies on the influence of formulation factors on the in vitro dissolution behaviour of such capsules have been published (Newton 1972, Newton et al 1971, Newton & Razzo 1974). Attention has also been drawn to the influence of the gelatin capsule on the bioavailability of a drug (Kranz et al 1977). However, there seems to be limited information available on disintegration in vivo. This may partly be due to the difficulty in performing such in vivo tests and the lack of useful methods. In an often cited study, Eckert (1976) used capsules filled with $NaHCO_3$ and determined the disintegration time by the change in pH of the gastric juice. He found that the content was released in 2·5 to 6 min. Recently, a new method using ^{99}Tcm and external scintigraphy was presented (Casey et al 1976). The study was based on few observations, but the authors reported a disintegration of 30–40 min for a capsule with an insoluble content and 6 min for a capsule containing a more soluble formulation.

In this communication we present data on the in vivo disintegration of gelatin capsules in fasting humans using a profile scanning technique (Alpsten et al 1976). Two different acetylsalicylic acid (ASA) formulations were studied. Formulation 1 consisted of 500 mg of ASA granules, 0·5–1 mm, dispensed in a hard gelatin capsule (Capsugel size 0+). Formulation 2 was similar to the first one but the granules were coated with an acid-resistant film (5% ASA was released in 2 h using the U.S.P. rotating basket procedure, 150 rev min^{-1} 0·1 M HCl). The ASA granules were marked by granulation with a radionuclide ^{51}Cr (1·85 MBq/50 μCi). The radiation was measured externally by using a moveable detector in a low activity laboratory (Sköldborn et al 1972). The method permitted determination of the position and distribution of the source within the body. The capsules were considered to have disintegrated when the point source (^{51}Cr) changed from the approximate punctate shape to a broadly distributed source (Alpsten et al, be published).

The subjects, who had fasted for 10 h, swallowed one capsule together with 100 ml of water following a cross-over design. During the measurements the volunteers were sitting in an armchair in a well-defined position while the detector was scanned back and forth repeatedly. After four such scans, corresponding to about 15 min, a break of about 5 min was made and the volunteer was allowed to move about freely. The complete 20 min cycle was repeated as long as was needed to register the disintegration of the capsule.

The disintegration time of the capsules in vitro was 1–2 min according to the official method of the British Pharmacopoeia 1973 and 2–4 min according to the method of Pharm. Nord. There was no difference in the in vitro disintegration time between the two formulations. The in vivo results are summarized in Table 1 and show that the disintegration, i.e. dispersion in the stomach, is slower than that observed in the two in vitro tests. There was an interindividual variation in the in vivo disintegration time of the capsules of 8–25 min for formulation 1 and 12–20 min for formula-

Table 1. Disintegration time of gelatin capsules in vivo

Subject	Formulation 1 ASA-granules	Formulation 2 enteric-coated ASA-granules
1	25	20
2	8	26
3	20	12
4	8	12
5	—	20
6	12	20
Mean	15	18

‡Correspondence

tion 2. Our results are not in agreement with those of Eckert (1976), who found a much faster disintegration time of hard gelatin capsules in vivo. However, the discrepancy might be explained by the findings of Casey et al (1976) which suggests that the in vivo dispersion time of hard gelatin capsules is dependent on the solubility of the content of the capsule. Both uncoated and coated ASA can be regarded as insoluble in relation to the $NaHCO_3$ used by Eckert. Another important factor in the latter study is probably the formation of CO_2, which could be expected to give a very fast dispersion of the content of the capsule.

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Are there opiate receptors in the invertebrates?

N. N. Osborne*, V. Neuhoff, *Max-Planck Institut fur experimentelle Medizin, Forschungsstelle Neurochemie Hermann-Rein-Str. 3, 3400 Göttingen, F.R.G.*

In the vertebrates it is thought that the regulation of dopamine neurons is influenced by morphine and morphine-like neuropeptides through opiate receptors (see Kuschinsky 1976). Naloxone can antagonize this influence. Furthermore high-affinity receptor binding occurs in the vertebrate but not in the invertebrate nervous system and because of this it has been suggested that opiate receptors do not exist in the invertebrates (Simantov et al 1976). This preliminary report shows that methionine-enkephalin has a specific effect on the dopamine neurons in the snail *Helix pomatia* which can be reversed by a previous injection of naloxone. This suggests that opiate receptors may indeed be present in the invertebrates.

Shells were removed from snails and 50 or 100 μg methionine-enkephalin in a volume of 0·1 ml snail saline (Meng 1960) injected directly into the auricle. Controls were injected with 0·1 ml saline alone while other animals received 0·1 ml saline together with either 100 μg naloxone or 100 μg naloxone plus 100 μg methionine-enkephalin. Forty min thereafter, the ganglia were dissected and analysed either for their dopamine or homovanillic acid (HVA) content, following the methods of Palkovits et al (1974) and Andén et al (1963).

The results showed that 50 μg methionine-enkephalin produced an increase in both dopamine (17·7 $\pm$ 2% n = 6) and HVA (14·9 $\pm$ 2% n = 8) compared with the controls which received only saline (dopamine concentration = 9 (s.d. 0·5; n = 10) and HVA concentration = 0·5 (s.d. 0·08 μg; n = 10)). Injection of 100 μg substance had an even greater effect, increasing the dopamine content by 26% s.d. 4% (n = 6) and the HVA content by 18·8% s.d. 3% (n = 8). Snails which received either methionine-enkephalin together with naloxone or naloxone alone showed no significant change (Students *t*-test) in their concentrations of dopamine or HVA.

The present data thus show that methionine-enkephalin can, as with vertebrates, alter the dopamine and HVA content in invertebrate nervous tissue and this can be antagonized by naloxone. This would therefore indicate the presence of opiate receptors in the invertebrates, although clearly more experiments are required to substantiate this. The effect of enkephalin on dopamine content and metabolism in the snail seems to be specific, since in preliminary initial experiments no alteration could be detected in the levels of either 5-HT or amino acids in the c.n.s. following methionine-enkephalin treatment.

During the preparation of this report, Stefano & Catapane (1978) independently observed that enkephalin can alter dopamine content in the invertebrate c.n.s.

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* Correspondence.