Since the depressor effect of arachidonic acid was fully reduced 30 min after indomethacin, it is suggested that PG synthesis was effectively reduced in our experimental conditions. Nevertheless, it may also be assumed that indomethacin is not only a PG synthesis inhibitor, but also has unspecific properties, such as spasmolytic activity. In these conditions, indomethacin would have to attenuate responses to most agonists. Since the depressor response to dopamine, but not to PGE_1 or sodium nitroprusside, was reduced by indomethacin at a dose reducing PG synthesis but without effect on mean arterial pressure, data may thus suggest that, in the anaesthetized rat, the depressor response to dopamine may be partly due to the release of a dilator PG.

These observations are not in agreement with those of Dressler, Rossi & Orzechowski (1975) and Pendleton & Woodward (1976) who claimed that indomethacin did not antagonize the renal response to dopamine in dogs. On the one hand, differences in the species used may account for these discrepancies: it seems that the vascular bed of the rat might be different from that of the dog in the response to dopamine, since after treatment by α-adrenoceptor blocking agents the depressor effect of the amine was inhibited by haloperidol and morphine, respectively (van Rossum, 1966; Dhasmana, Dixit & others, 1969), in dogs, but not affected by these agents in rats (Aihara, Kasai & Sakai, 1972). On the other hand, it seems that, according to the nature of the vascular wall, dopamine may or may not be able to induce PG release, since indomethacin failed to attenuate the renal vasodilator action of dopamine in dogs (Dressler & others, 1975; Pendleton & Woodward, 1976), but reduced the coronary dilator response to the amine in the same animal (Takenada & Morishita, 1972).

Our data also support the role of PG in the systemic depressor response to dopamine in the anaesthetized rat.

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REFERENCES

AIHARA, H., KASAI, A. & SAKAI, T. (1972). *Jap. J. Pharmac.*, **22**, 617–627.
DHASMANA, K. M., DIXIT, K. S., DAWAN, K. N. & GUPTA, G. D. (1969). *Ibid.*, **19**, 168–169.
DRESSLER, W. E., ROSSI, G. V. & ORZECHOWSKI, R. F. (1975). *J. Pharm. Pharmac.*, **27**, 203–204.
EBLE, J. N. (1964). *J. Pharmac. exp. Ther.*, **145**, 64–70.
GOLDBERG, L. I. (1972). *Pharmac. Rev.*, **24**, 1–29.
GOLDBERG, L. I. (1975). *Biochem. Pharmac.*, **24**, 651–653.
PENDLETON, R. G. & WOODWARD, P. (1976). *Archs int. Pharmacodyn. Thér.*, **221**, 250–260.
TAKENADA, F. & MORISHITA, H. (1976). *Ibid.*, **222**, 81–93.
VAN ROSSUM, J. M. (1966). *Ibid.*, **160**, 492–494.

Bioavailability of phenytoin in lipid containing dosage forms in rats

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Phenytoin, a poorly water soluble drug, is erratically absorbed after oral administration in solid dosage form (Glazko & Chang, 1972; Lund, 1974). It has been reported that the bioavailability after oral administration of poorly water soluble drugs, particularly those that are lipophilic, can be improved by co-administration of lipid material (Greco, Moss & Foley, 1959; Crounse, 1961; Kraml, Dubue & Beall, 1962; Kabasakalian, Katz & others, 1970). There are no reports on the effect on the bioavailability of phenytoin when it is co-administered with vegetable oil or given in an emulsion form. Therefore, we have examined in rats the absorption profile of micronized phenytoin after its oral administration as an aqueous suspension, a corn oil suspension or a corn oil emulsion. The dosage forms of phenytoin (particle size 0·32 μm) were prepared in a suitable vehicle (Table 1). The corn oil emulsion was prepared by trituration and finally passing through a homogenizer; the suspensions were prepared by stirring with a mechanical stirrer. Each preparation was agitated at room temperature for 24 h before administration to ensure that the vehicles were saturated with phenytoin. The solubility of phenytoin in the different vehicles was measured by filtering through G-4 sintered glass filters and diluting the filtrate with 0·1 M NaOH; the absorbance was measured at 230 nm against a suitable blank.

Adult male albino rats, 300 to 340 g, were fasted for 20 h before and 12 h after drug administration. Phenytoin (20 mg kg^{-1}) in 0·5 to 1·2 ml of dosage form was placed in the stomach via a metal catheter, each dosage form was given to six rats. At 0·5; 1; 2; 3; 5; 7 and 12 h after administration, blood samples (0·3 ml) were collected from the tail vein. Serum was separated and frozen to −20° until radioimmunoassay (Cook, Kepler & Christensen, 1973). Serum concentrations were plotted against time and the area under the curve (AUC) was calculated by the trapezoidal rule. For

* Correspondence.

comparison of the results, Student's *t*-test for unpaired observations was used.

The effect of lipid on the bioavailability of phenytoin is apparent from Fig. 1. After administration of corn oil emulsion and corn oil suspension, the maximal concentration is reached more slowly (Fig. 1 and Table 2) than with the aqueous suspension. However, the magnitudes of the mean drug serum peaks from corn oil emulsion and corn oil suspension are approximately 1·89 and 1·47 times higher than, and are significantly different ($P < 0.01$) from aqueous suspension. The AUCs (0–12 h) calculated from serum concentrations obtained from corn oil suspension and emulsion are significantly higher than that for the aqueous suspension ($P < 0.01$). It is evident from Table 1 that the difference between the vehicles cannot be attributed to the solubility of phenytoin at the time of dosing.

Table 1. *Composition of dosage forms of phenytoin and solubility of phenytoin in the different dosage forms.*

Vehicle	Composition[a] content ml^{-1}	Phenytoin solubility in vehicle (μg ml^{-1})
Aqueous suspension (0·5% methyl cellulose)	6 mg phenytoin 10 mg polysorbate 80	52
Corn oil suspension	12 mg phenytoin 10 mg polysorbate 80	63
Corn oil emulsion	12 mg phenytoin 0·4 g corn oil 10 mg polysorbate 80 (to 1 ml with H_2O)	74

[a] Phenytoin B.P.C., polysorbate 80, Belg. Ph., Corn oil U.S.P. grade.

Table 2. *Serum peak* (C_{max}), *time to peak* (T_{max}) *and area under curve (AUC)* (0–12 h) *following oral administration of different dosage forms to six rats in each group**.

Dosage form	Cmax (μg ml^{-1})	Tmax (h)	AUC (μg ml^{-1} h^{-1})
Aqueous suspension (A)	1·71 ±0·18	0·83 ±0·24	7·09 ±0·58
Corn oil suspension (B)	2·53 ±0·16	2·66 ±0·38	9·87 ±0·35
Corn oil emulsion (C)	3·24 ±0·04	2·50 ±0·29	12·7 ±0·39
	A *vs* B : $P < 0.01$ B *vs* C : $P < 0.05$ A *vs* C : $P < 0.01$	A *vs* B : $P < 0.01$ B *vs* C : N.S. A *vs* C : $P < 0.01$	A *vs* B : $P < 0.01$ B *vs* C : $P < 0.01$ C *vs* A : $P < 0.05$

* Mean values (± s.e.m.) are given.

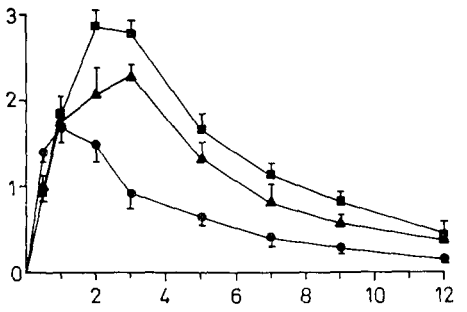

FIG. 1. Mean serum concentration of phenytoin as a function of time following oral administration of 20 mg kg^{-1} dose in the form of an aqueous suspension ●—●, a corn oil suspension ▲—▲ and a corn oil emulsion ■—■, each to six rats. Vertical bars indicate standard error of the mean. Ordinate: Phenytoin concentration in serum (μg ml^{-1}). Abscissa: Time (h).

The differences in absorption among different dosage forms may be explained by physiological or physicochemical mechanisms (Bates, Gibaldi & Kanig, 1966; Bates, Gibaldi & Lin, 1967; Carrigan & Bates, 1973; Bates & Sequeira, 1975); delay in gastric emptying with increased bile secretion, e.g. initiates faster dissolution from the lipid dosage form (Carey & Small, 1972; Holt, 1972). These results with the emulsion dosage form could be of interest for formulating a palatable liquid dosage form of phenytoin for children.

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REFERENCES

BATES, T. R., GIBALDI, M. & KANIG, J. L. (1966). *Nature*, **210**, 1331–1333.

BATES, T. R., GIBALDI, M. & LIN, S. L. (1967). *J. pharm. Sci.*, **56**, 1492–1495.

BATES, T. R. & SEQUEIRA, J. A. (1975). *Ibid.*, **64**, 793–797.

CARRIGAN, P. J. & BATES, T. R. (1973). *Ibid.*, **62**, 1476–1479.

COOK, C. E., KEPLER, J. A. & CHRISTENSEN, H. D. (1973). *Res. Commun. chem. Path. Pharmac.*, **5**, 767–774.

CAREY, M. C. & SMALL, D. M. (1972). *Archs intern. Med.*, **130**, 506–509.

CROUNSE, R. G. (1961). *J. invest. Derm.*, **37**, 529–532.

GLAZKO, A. J. & CHANG, T. (1972). In: *Antiepileptic Drugs*, p. 127–136. Editors: Woodbury, D. M., Penry, J. K. & Schmidt, R. D. New York: Raven Press.

GRECO, G. A., MOSS, E. L., JNR. & FOLEY, E. J. (1959–60). *Antibiot. A.*, **7**, 663–666.

HOLT, P. R. (1972). *Archs intern. Med.*, **130**, 574–578.

KABASAKALIAN, P., KATZ, M., ROSENKRANTZ, B. & TOWNLEY, E. (1970). *J. pharm. Sci.*, **59**, 595–600.

KRAML, M., DUBUE, J. & BEALL, D. (1962). *Can. J. Biochem. Physiol.*, **40**, 1449–1453.

LUND, L. (1974). *Eur. J. clin. Pharmac.*, **7**, 119–124.