derived from the BUT-viscosity curves for individual rabbits. It is apparent that none of the polymers offers outstanding BUT at a viscosity acceptable for artificial tears. The six commercial artificial tears tested gave BUT values ranging from 64·5 s (s.e.m. 7·7) to 113·6 s (s.e.m. 18·4).

Drainage and dilution by tear secretion, even when diminished in pathological states, may be expected to reduce the concentration of exogenously applied polymer solutions quite rapidly, and it is concluded that materials capable of producing more stable artificial pre-ocular films should be sought.

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Influence of stomach emptying rate on tissue radioactivity after [^{14}C]imipramine in the rat

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As large as 36-fold differences in steady state plasma concentrations of tricyclic antidepressant compounds have been reported in patients given the same oral dosing regimen (Hammer & Sjöqvist, 1967). Several pharmacokinetic factors have been postulated to contribute to these differences. These include individual variation in liver metabolism (Hammer & Sjöqvist, 1967; Alexanderson & Borga, 1973), plasma protein binding (Alexanderson & Borga, 1972; Glassman, Hurwic & Perel, 1973) and first pass metabolism (Gram & Christiansen, 1975). Most investigators, however, have assumed individual variation in gastrointestinal absorption to be unimportant (Haydu, Dhrymiotis & Quinn, 1962; Kragh-Sørensen, Hansen & others, 1974).

An opportunity to test the relative importance of individual variation in metabolism or absorption on tissue concentrations of imipramine (with its metabolites) was provided from data obtained in a study concerning the effects of tranquillizers on [^{14}C]imipramine pharmacokinetics (Beaubien, Mathieu & Coldwell, 1975). One of the experiments utilized non-anaesthetized male Wistar rats with bile fistulas and which were orally administered either thioridazine (16 mg kg^{-1}), diazepam (10 mg kg^{-1}) or 0·25% (w/v) gum tragacanth solution (controls) 40 min before [^{14}C]imipramine; dosing volumes were 5 ml kg^{-1} in each instance. The animals were decapitated 90 min after [^{14}C]imipramine dosing. Although thioridazine reduced the biliary elimination of radioactivity as a result of inhibition of stomach emptying, diazepam had no measurable effect on imipramine pharmacokinetics except perhaps to slightly enhance the intestinal absorption of radioactive drug. Because the rate limiting step in gastrointestinal absorption of radioactivity was the velocity of stomach emptying rather than intestinal absorption rate (see below), the diazepam-pretreated animals (n = 5) were grouped with the controls (n = 5) in testing for a mechanism which caused variation between individuals in tissue concentrations of radioactivity.

Correlation coefficients were obtained between tissue concentrations of ^{14}C and the amount of radioactivity contained at absorption sites or in excreta 90 min after [^{14}C]imipramine administration. It was reasoned that a significant negative correlation should result between tissue radioactivity concentrations and the total amount of ^{14}C label in either absorption or elimination pools if the rate constants from or to these pools exerted a strong controlling influence. A significant positive correlation would indicate that both tissue and pool radioactivity concentrations were controlled by the same mechanism.

Table 1 shows that at 90 min after [^{14}C]imipramine dosing a positive correlation existed between radioactivity in the bile and urine. A weak positive correlation also existed between bile and tissue radioactivity although this was statistically insignificant. The fact that a negative correlation of tissue radioactivity with that of bile did not occur indicates that individual variation in biliary elimination of imipramine and its metabolites played only a minor role in causing differences in tissue concentrations of radioactivity within the 90 min time period. This is remarkable in that 57·0 ± 2·79% (mean ± s.e.) of all the absorbed radioactivity (calculated as the sum of ^{14}C in all the tissues, bile and urine) was recovered in the bile by this time. Biliary excretion was

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the most important route of elimination since only 3·33 ± 0·37% of absorbed radioactivity was found in the urine. The negligible influence of urinary elimination on tissue ^{14}C concentrations in this preparation is further emphasized by the high positive correlation of urinary and tissue radioactivity (Table 1).

Table 1. *Correlation of eliminated or unabsorbed radioactivity with that found at various sites 90 min after [^{14}C]-imipramine dosing.*

Site	Correlation coefficient			
	Bile (90 min collection)	Urine (90 min collection)	Stomach contents	Small intestinal contents
Plasma	+0·57	+0·86**	−0·72*	+0·57
Brain	+0·55	+0·68*	−0·84**	+0·45
Heart	+0·40	+0·67*	−0·74*	+0·71*
Liver	+0·49	+0·88***	−0·77**	+0·72*
Kidneys	+0·51	+0·79**	−0·82**	+0·67*
Lungs	+0·12	+0·45	−0·49	+0·57
Muscle (femur)	+0·48	+0·63*	−0·72*	+0·48
Fat (perirenal)	+0·59	+0·75*	−0·75*	+0·33
Bile (90 min collection)	—	+0·68*	−0·80**	−0·14
Urine (90 min collection)	+0·68*	—	−0·83**	+0·50
Stomach contents	−0·80**	−0·83**	—	−0·31
Small intestine contents	−0·14	+0·50	−0·31	—

^{14}C radioactivity was expressed as μg ml^{-1} or μg g^{-1} of imipramine for plasma or tissues. It was expressed as μg of imipramine kg^{-1} of body weight for stomach contents, small intestinal contents, and 90 min bile and urine collections. Group size was 10 animals.
* $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

The radioactivity of plasma, tissues, bile and urine showed a high negative correlation with the amount of radioactivity remaining in the stomach (Table 1). The major factor determining plasma and tissue concentrations of radioactivity must therefore have been the rate of elimination of [^{14}C]imipramine from the stomach. This in turn was probably related to the rate of stomach emptying since the correlation coefficient between the weight of the stomach contents (expressed as mg kg^{-1} of body weight) and the retention of radioactivity by the stomach was 0·79, $P < 0.01$. The radioactivity of small intestine contents was positively correlated with tissue ^{14}C concentrations (Table 1) indicating that the intestinal absorption rate was rapid and exerted no strong control over the amount of drug reaching the tissues. The correlation of lung radioactivity to the amount of ^{14}C in absorption or elimination pools was insignificant in each instance. This was probably the result of the strong accumulation process(es) in lung for imipramine (Junod, 1972) which overshadowed absorption and elimination factors.

The approximate concentration ratio of radioactivity in stomach contents to that of plasma was 1500 to 1 whereas it was only 40 to 1 for small intestinal contents 90 min after oral administration. This indicates that imipramine is very poorly absorbed from the stomach and must first travel to the small intestine before it can rapidly enter the systemic circulation. Individual differences in the rate of gastric emptying can therefore be expected to have a major influence on plasma and tissue concentrations of imipramine (and also desipramine). Tissues such as the brain would contain mainly imipramine and desipramine (Bickel & Weder, 1968). It can therefore be assumed that the concentrations of these two substances in the plasma were also greatly influenced by the rate of gastric emptying since tissue and plasma tricyclic antidepressant concentrations have been shown to vary in the same direction (Gram, Christiansen & Overø, 1974).

Gastric emptying rate has been found to be extremely variable in man (Heading, Nimmo & others, 1973). In view of this, the results obtained in the present study should have some bearing on plasma and tissue concentrations of tricyclic antidepressants in the clinical situation. Whether or not differences in gastric emptying rates exert a significant influence on steady state plasma concentrations of tricyclic antidepressants remains to be determined.

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