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Effects of Ageing on the Oral Absorption of D-Xylose in Rats

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Abstract

The effects of ageing on the oral absorption of D-xylose were investigated in rats.

The pharmacokinetic analysis of D-xylose concentration in plasma after oral administration showed that the fraction absorbed was increased to $0{\cdot}998 \pm 0{\cdot}002$ and $0{\cdot}950 \pm 0{\cdot}049$, respectively, in old (52 weeks) and very old (102 weeks) rats, compared with $0{\cdot}768 \pm 0{\cdot}052$ in young (9 weeks) rats, while the absorption rate constant was not significantly changed: $0{\cdot}944 \pm 0{\cdot}233$, $0{\cdot}844 \pm 0{\cdot}143$ and $0{\cdot}725 \pm 0{\cdot}004\ h^{-1}$, respectively, in young, old and very old rats. The absorbed fractions estimated from faecal and urinary excretion were in agreement with those by the pharmacokinetic analysis. Thus, the present study demonstrated an increase in the extent of the oral absorption of D-xylose with ageing. The increase in the extent of absorption might be caused by a delay in the intestinal transit, because the absorption rate constant was unchanged.

These results suggest potential increases with ageing in the fractions absorbed of hydrophilic drugs such as D-xylose where oral absorption is incomplete.

As reviewed by Schmucker (1985), age-dependent changes in gastrointestinal drug absorption have not been documented extensively, or have been left largely inconclusive. Although a number of gastrointestinal functions which may affect gastrointestinal absorption, such as gastric acid secretion, splanchnic blood flow, gastrointestinal motility and number and absorptive capacity of the enterocytes, have been suggested to change with age, the effects of ageing on drug absorption have not been fully understood in relation to the age-dependent changes in those gastrointestinal functions.

The intestinal absorption of nutrients, such as glucose and amino acids, has been relatively well investigated with regard to the effects of ageing, and appears to be generally reduced with ageing because of reductions in active transport (Thomson 1979; Schmucker 1985; Freeman & Quamme 1986; Gastaldi et al 1992; Vinardell 1992; Ferraris et al 1993), although age-dependent changes in the maximum transport rate, the Michaelis constant and the passive transport coefficient are not always consistent, and several studies (Said & Hollander 1984; Schmucker 1985) failed to show age-dependent changes.

The effects of ageing on passive transport are less clear. The intestinal absorption of lipophilic and highly membrane-permeable compounds was reportedly increased with ageing in perfusion studies in rats (Schmucker 1985). However, the increase in the absorption may be ascribable to a reduction in the aqueous diffusional resistance (or the resistance of the unstirred water layer), which is the major absorption barrier for those compounds with high membrane permeability. The age-dependent changes in the intrinsic intestinal membrane permeabilities of those compounds are so far unknown. Furthermore, the significant involvement of the aqueous diffusional resistance in the intestinal absorption may be questionable in-vivo, where the diffusional resistance may be extensively reduced by more efficient intestinal motility, compared with perfusion, making the implication of the increased intestinal absorption in perfusion for in-vivo absorption unclear. The orally absorbed fractions of hydrophilic and poorly membrane-permeable compounds, mannitol and polyethylene glycol (PEG) 400 (Ma et al 1992) or low molecular weight components (molecular weight below 400) of PEG 400 (Lin & Hayton 1983b), were reportedly increased with ageing in rats. A delay in the intestinal transit was suggested to be at least partly responsible for the increases in the fraction absorbed (Lin & Hayton 1983a). The aqueous diffusional resistance is unlikely to be significantly involved in the intestinal absorption of those poorly membrane-permeable compounds in any conditions. However, another possibility of an increase in the intestinal membrane permeability is yet to be evaluated. Lin & Hayton (1983b) also reported that the fractions absorbed of high molecular weight components (molecular weight above 400) of PEG 400 were decreased with ageing, conversely to the increase for the lower molecular components, and suggesting a molecular weight-dependent difference in the effect of ageing on the intestinal membrane permeability of PEG. This may be explained by a molecular weight dependency in the relative contributions of transcellular and paracellular pathways in the intestinal transport of PEG and a difference in the age-dependent changes in the permeabilities of those pathways. Similarly, the effects of ageing on the intestinal membrane permeability of lipophilic compounds, which are presumed to be primarily transported by a transcellular pathway, may not be necessarily the same as those for hydrophilic compounds. Although the apparent rates of absorption of several drugs have been reported to be unchanged with ageing (Schmucker 1985), it may not lead

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to unchanged intestinal membrane permeability because potential changes in gastric emptying have not been evaluated.

D-Xylose has been clinically used to assess intestinal absorptive function, and subjected to exceptionally extensive evaluation of age-dependent changes in its oral absorption (Schmucker 1985; Craig & Atkinson 1988). D-Xylose is a hydrophilic compound, and reported to be passively absorbed in rats (Ohkohchi & Himukai 1984). However, the fraction absorbed of D-xylose has been reported to be unchanged with ageing in man (Weiner et al 1984; Johnson et al 1985, 1986; Schmucker 1985), inconsistent with the aforementioned reports of increased fractions absorbed for other hydrophilic compounds, PEG 400 and mannitol, in rats. The apparent absorption rate constant of D-xylose has been suggested to be either unchanged (Johnson et al 1985, 1986) or decreased (Weiner et al 1984) with ageing. We, therefore, conducted a pharmacokinetic study in rats for more extensive evaluation of age-dependent changes in the oral absorption of D-xylose in an effort to clarify the effects of ageing on oral drug absorption and meet ever increasing demands for optimizing dosage regimens for an increasingly aged population.

Materials and Methods

Materials

D-[U-^{14}C]Xylose (1·7 GBq mmol^{-1}) was purchased from Amersham International plc (Buckinghamshire, UK). Biofluor and Scintisol EX-H, scintillation fluids, were purchased from DuPont-NEN Co. (Boston, MA, USA) and Dojindo Lab. (Kumamoto, Japan), respectively. Soluene-350, a tissue solubilizer, was purchased from Packard Instrument Co., Inc. (Meriden, CT, USA). D-Xylose was purchased from Sigma Chemical Co. (St Louis, MO, USA). All other chemicals were of analytical grade and commercially obtained.

Animals

Male Wistar rats were used after fasting overnight. Their ages and weights were as follows: young, 9 weeks and 273 ± 5 g; old, 52 weeks and 537 ± 13 g; very old, 102 weeks and 558 ± 22 g.

Oral absorption experiments

Male Wistar rats of various ages were cannulated in the right jugular vein under light ether anaesthesia. After regaining consciousness, and allowing a recovery period of 1 h, each rat was given an oral dose (100 mg/5 mL kg^{-1} or 300 kBq kg^{-1}) of [^{14}C]D-xylose, which was dissolved in saline, using a gastric tube, left free in a metabolic cage at an ambient temperature of 25°C; 250 μL of blood was taken periodically through the cannula. The blood was centrifuged for 3 min with a Microfuge B (Beckman Instruments, Palo Alto, CA, USA) to obtain plasma. One hundred microlitres of plasma was placed in a counting vial, to which was added 3 mL Biofluor, to determine the radioactivity with a liquid scintillation counter (LSC-1000, Aloka Co., Tokyo, Japan).

Urine was collected over the intervals 0–3, 3–5 and 5–24 h. At the end of each period, the rat was forced to smell ether, soaked into absorbent cotton, to induce urination. Each sample of urine was diluted to 25 or 50 mL, and 100 μL aliquot was taken for the determination of radioactivity in the same way as plasma samples.

Faeces was collected for 24 h after administration, weighed in a tared counting vial, mixed with 10 μL saline, and homogenized with a spatula. Approximately 150 mL homogenized sample was placed in a tared counting vial to determine its weight, mixed with 1 mL Soluene-350, a tissue solubilizer, to solubilize at 55°C for 2 h, and then mixed with 0·2 mL 30% hydrogen peroxide to decolorize at 55°C for 30 min. After adding 5 mL Scintisol EX-H, and then 0·2 mL 1 M HCl, the radioactivity was determined.

Each rat was killed 24 h after administration, and the entire gastrointestinal tract was isolated. The contents of the stomach, small intestine, caecum and large intestine were rinsed out with 3, 5, 3 and 2 mL saline, respectively. Each sample was collected in a tared counting vial to determine its weight, and homogenized with a Polytron homogenizer with a PT10 shaft (Kinematica GmbH, Switzerland). One hundred microlitres each of the homogenized samples was placed in a counting vial, and mixed with 3 mL Biofluor to determine its radioactivity.

A series of intravenous administration experiments was conducted at the same dose as the oral dose to characterize the distribution and elimination profiles of D-xylose.

Data analysis

Plasma concentration (C) vs time (t) profiles of D-xylose were analysed by a two-compartment model with first-order absorption (Wagner 1993), where the plasma concentrations after oral and intravenous administration are described by equations 1 and 2, respectively.

$$C = L \cdot e^{-\alpha t} + M \cdot e^{-\beta t} - N \cdot e^{-k_a t} \quad (1)$$

$$C = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \quad (2)$$

where

$$L = \frac{A \cdot F \cdot k_a}{k_a - \alpha} \quad (3)$$

$$M = \frac{B \cdot F \cdot k_a}{k_a - \beta} \quad (4)$$

$$N = L + M \quad (5)$$

and where k_a and F are the absorption rate constant and fraction absorbed, respectively. The first and the second term in equation 2 characterize the distribution and elimination phase, respectively, with the apparent rate constants of α and β ($\alpha > \beta$) and the constants of A and B. The values of A, B, α and β were estimated by fitting equation 2 to the concentration vs time profiles after intravenous administration using a nonlinear regression program, PCNONLIN (Statistical Consultants, Inc., Lexington, KY, USA; Gentleman 1986). The k_a and F values were estimated by fitting equation 1 to the concentration vs time profiles after oral administration using PCNONLIN, with A, B, α and β fixed at the values estimated by the analysis of the data after intravenous administration. The half-life of the β phase ($t_{\frac{1}{2}\beta}$), the distribution volume of the central compartment (Vd_1), the steady-state distribution volume (Vd_{ss}), the total body

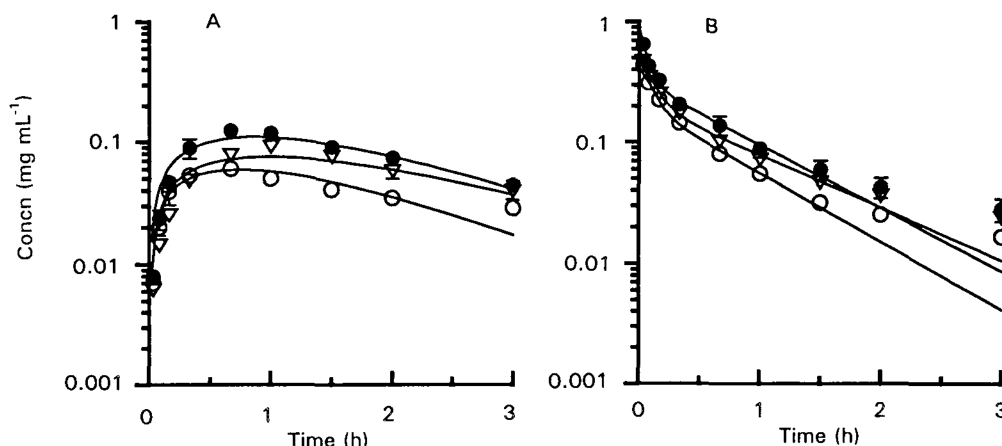

FIG. 1. Plasma concentrations vs time profiles of D-xylose after oral (A) and intravenous (B) administration in young (○), old (●) and very old (▽) rats. Data are the mean ± s.e. (n = 3). The dose was 0·1 g kg^{-1} in 5 mL.

clearance (CL_{tot}) and the renal clearance (CL_r) were calculated as follows:

$$t_{\frac{1}{2}\beta} = \ln 2/\beta \qquad (6)$$

$$Vd_1 = \frac{Dose}{A + B} \qquad (7)$$

$$Vd_{ss} = \left(\frac{k_{12}}{k_{21}} + 1\right)/Vd_2 \qquad (8)$$

$$CL_{tot} = \frac{Dose}{AUC_\infty} \qquad (9)$$

$$CL_r = \frac{X_{u,3}}{AUC_3} \qquad (10)$$

where k_{12} and k_{21} are the microscopic rate constants for the transfer from the central compartment to the peripheral and the peripheral to the central, respectively. The ratio of k_{12} to k_{21} can be expressed in terms of A, B, α and β as follows:

$$\frac{k_{12}}{k_{21}} = \frac{A \cdot B \cdot (\alpha - \beta)^2}{(A \cdot \beta + B \cdot \alpha)^2} \qquad (11)$$

$X_{u,3}$ represents the cumulative urinary excretion in 3 h. The AUC_∞ and AUC_3 terms represent the area under the concentration vs time curves from 0 h to infinity and 0 to 3 h, respectively. The AUC values were obtained by integrating equation 2.

The fraction absorbed (F) was also estimated from faecal and urinary excretion. The cumulative faecally-excreted fraction in 24 h after administration was subtracted from 1 to estimate F. The faecal excretion was assumed to be almost completed by 24 h after administration, because the recovery of D-xylose from the entire gastrointestinal tract was only 4–7% of the dose and independent of age. The cumulative urinary excreted fraction in 24 h after oral administration was normalized by that after intravenous administration to estimate F.

Results

D-Xylose concentration in plasma

Fig. 1 shows the plasma concentration vs time profiles of D-xylose after oral and intravenous administration in young, old and very old rats. The D-xylose concentration after oral administration tended to be higher in old and very old rats than in young rats. The maximum concentrations (C_{max}) after oral administration were 0·061 ± 0·004, 0·125 ± 0·012 and 0·095 ± 0·009 mg mL^{-1}, respectively, in young, old, and very old rats, and significantly higher in old and very old rats than in young rats, while the difference in C_{max} between old and very old rats were insignificant. The D-xylose concentration after intravenous administration also tended to be higher in old and very old rats than in young rats, suggesting

Table 1. Effects of ageing on the pharmacokinetic parameters of D-xylose distribution and elimination after intravenous administration in rats.

Parameters	Young	Old	Very old
A (mg mL^{-1})	0·360 ± 0·035	0·570 ± 0·037**	0·378 ± 0·015
B (mg mL^{-1})	0·203 ± 0·012	0·315 ± 0·021***	0·213 ± 0·009
α (h^{-1})	11·9 ± 1·2	15·7 ± 1·9	10·0 ± 0·7
β (h^{-1})	1·3 ± 0·1	1·2 ± 0·3	1·0 ± 0·1
$t_{\frac{1}{2}\beta}$(h)	0·56 ± 0·04	0·62 ± 0·12	0·72 ± 0·04*
Vd_1 (mL kg^{-1})	179 ± 8	113 ± 3***	169 ± 7
Vd_{ss} (mL kg^{-1})	356 ± 10	248 ± 27***	348 ± 39
CL_{tot} (mL h^{-1} kg^{-1})	517 ± 27	335 ± 54*	386 ± 6***
CL_r (mL h^{-1} kg^{-1})	320 ± 45	202 ± 44	196 ± 43

Data are the mean ± s.e. (n = 3). *$P < 0·05$; **$P < 0·02$; ***$P < 0·01$ compared with the values for young rats.

Table 2. Effects of ageing on the pharmacokinetic parameters of D-xylose absorption in rats.

Parameters	Young	Old	Very old
k_a (h^{-1})	0·944±0·233	0·844±0·143	0·725±0·004
F (model analysis)	0·768±0·052	0·998±0·002**	0·950±0·049†
(faecal excretion)	0·817±0·013	0·956±0·016***	0·939±0·029*
(urinary excretion)[a]	0·620±0·025	0·980±0·040***	0·779±0·028**

Data are the mean ± s.e. (n = 3). [a]Normalized by the urinary recovery after intravenous administration. *$P < 0·05$; **$P < 0·02$; ***$P < 0·01$; †$P < 0·10$ compared with the values for young rats.

age-dependent changes in the distribution or elimination of D-xylose. Therefore, pharmacokinetic analysis was required to determine if age-dependent enhancement of absorption was involved in the increases in D-xylose concentration after oral administration in aged (old and very old) rats.

Pharmacokinetic analysis of D-xylose disposition

The concentration vs time profiles were satisfactorily described by a two-compartment model (intravenous administration) and a two-compartment model with first-order absorption (oral administration), although the concentrations deviated slightly at later times (2 and 3 h) after intravenous administration. Tables 1 and 2 summarize the pharmacokinetic parameters of D-xylose distribution and elimination, and those of D-xylose absorption, respectively, estimated by using a two-compartment model with first-order absorption. The increases in D-xylose concentration after intravenous administration in aged rats, compared with that in young rats, were attributed to decreases in the volumes of distribution, Vd_1 and Vd_{ss}, in old rats and an increase in the half-life of the elimination (β) phase, $t_{\frac{1}{2}\beta}$, in very old rats. The total clearance (CL_{tot}) was accordingly decreased in aged rats. The decreases in CL_{tot} in aged rats, compared with that in young rats, were comparable with those in renal clearance (CL_r), the major elimination route of D-xylose. Although the decreases in CL_r were not statistically significant, it is most likely that the decreases in CL_{tot} were attributable to the decreases in CL_r, suggesting declined renal functions in aged rats.

As for oral absorption, increases in fraction absorbed (F) were shown to be involved in the increases in D-xylose concentration in plasma in aged rats (Table 2), but the absorption rate constant (k_a) was unchanged. D-Xylose was suggested to be almost completely absorbed in old and very old rats by pharmacokinetic model analysis, while about three-quarters of the dose was suggested to be absorbed in young rats. The F values were in good agreement with those estimated from faecal and urinary excretion, though the F values from urinary excretion appeared to be slightly underestimated in young and very old rats.

Urinary excretion of D-xylose

Significant amounts of D-xylose were excreted in urine by 3 h after administration in both intravenous and oral administration experiments and in all ages of rats as shown in Table 3. Thereafter, D-xylose was excreted more slowly, and the urinary recovery was incomplete even up to 24 h after intravenous administration in all age groups. The values in Table 3 were all comparable with those estimated by a colorimetric method by Eberts et al (1979), suggesting insignificant metabolism of D-xylose and justifying the use of radioactivity measurements for characterizing D-xylose disposition. The latter values were approximately 90% of the former values, and similar results were obtained for plasma 40 min after administration.

The urinary excretion after oral administration was increased in old rats but not in very old rats, compared with young rats. However, the fraction absorbed (F) as the urinary excreted fraction normalized by that after intravenous administration was increased in both old and very old rats (Table 2). Thus, the urinary excretion, which is used as a measure of intestinal absorptive function in the xylose test, may not even qualitatively reflect absorptive functions, unless normalized by the urinary excretion after intravenous administration.

Table 3. Effects of ageing on the urinary excretion of D-xylose in rats.

Route	Age	Cumulative urinary excretion (% of dose)		
		3 h	5 h	24 h
Intravenous	Young	61·4±5·7	73·9±1·6	80·1±0·8
	Old	59·6±4·5	62·2±3·5 *	70·2±6·0
	Very old	50·8±11·7	52·9±13·6	68·0±6·5
Oral	Young	38·2±0·4	41·7±1·3	49·7±2·0
	Old	54·9±4·0**	54·9±4·0*	68·8±2·8***
	Very old	36·1±4·0	36·1±4·0	53·0±1·9

Data are the mean ± s.e. (n = 3). *$P < 0·05$; **$P < 0·02$; ***$P < 0·01$ compared with the values for young rats.

Discussion

The fraction absorbed of D-xylose was shown to be increased with ageing in rats, in agreement with the reports for PEG 400 and mannitol (Lin & Hayton 1983b; Ma et al 1992). In addition, we found that the absorption rate constant of D-xylose was unchanged. Assuming that the gastric emptying rate constant of D-xylose is similar to that of 3·48 h^{-1} reported for L-glucose (Yuasa et al 1994), the absorption rate constant of 0·944 h^{-1} in young rats would be smaller than the gastric emptying rate constant, suggesting that the oral absorption rate of D-xylose is largely restricted by intestinal absorption rather than gastric emptying. Therefore, the unchanged absorption rate constant may suggest an unchanged rate of intestinal absorption, and the increases in the fraction absorbed in aged (old and very old) rats may be primarily brought about by a delay in intestinal transit, as suggested by Lin & Hayton (1983a). The observation of the decreased absorption rate constant but unchanged fraction absorbed of D-xylose with ageing in man (Weiner et al 1984) can also be explained by a delay in the intestinal transit. Thus, intestinal transit appears to be persistently delayed with ageing, resulting in increased or maintained fractions absorbed. So far unexplained are the reasons why the effects of ageing on the absorption rate constant were different between these studies, and the observation of unchanged rate, as well as extent, of absorption of D-xylose in man by Johnson et al (1985, 1986), which suggests unchanged intestinal transit. Age-dependent changes in gastric emptying and intestinal absorption (or membrane permeability), as determinants of oral absorption, need to be re-examined.

The pharmacokinetic profile of D-xylose has not been reported in rats to our knowledge. The pharmacokinetic profile of D-xylose in young rats was similar to that in man (Craig & Atkinson 1988), in that the oral absorption was incomplete (about 70% absorbed), and it was primarily eliminated into urine as unchanged (about 60% of total clearance), assuring its usefulness as a marker for intestinal absorptive functions. The unrecovered fraction of 20% at 24 h after intravenous administration was comparable with the fraction metabolized to CO_2 in man (15%). The steady-state distribution volume (Vd_{ss}) of 356 mL kg^{-1} was about 50% larger than the extracellular fluid volume of 219 mL kg^{-1} (Tsuji et al 1985), measured as the Vd_{ss} of inulin, suggesting some extent of distribution in the intracellular space in addition to the primary distribution in the extracellular fluid. The renal clearance (CL_r) of 320 mL h^{-1} kg^{-1} was comparable with the glomerular filtration rate of 388 mL h^{-1} kg^{-1} (Tsuji et al 1985), measured as the CL_r of inulin, suggesting that glomerular filtration is the primary excretion mechanism of D-xylose in the kidney. The Vd_{ss} value was close to those reported in man, while both CL_{tot} and CL_r were about three times those in man (Johnson et al 1986). These features of distribution and renal excretion of D-xylose in rats are also in agreement with those in man (Craig & Atkinson 1988), except that the elimination was faster in rats as would be expected for elimination processes in smaller animals (Mordenti 1986).

The decreases in the CL_r of D-xylose, or glomerular filtration rate, in aged rats are in agreement with the generally accepted suggestions of declines in renal functions with ageing (Schmucker 1985). The decreases in the volumes of distribution (Vd_1 and Vd_{ss}) in old rats, compared with young rats, can be explained as the results of a decrease in body water relative to body weight, due to a loss of body water and a simultaneous increase in body fat with ageing. This age-dependent shift in body constituents has been suggested to explain the age-dependent decreases in the distribution volumes of hydrophilic drugs, such as antipyrine, and the increases in those of lipophilic drugs, such as diazepam (Schmucker 1985). The volumes of distribution in very old rats, however, were increased, compared with those in old rats, and similar to those in young rats. Although similar age-dependent changes in distribution volumes, and a decrease and subsequent increase, were reported for cefazolin and inulin by Tsuji et al (1985), the mechanism for the increase in very old rats is so far unknown. The Vd_{ss} was reported to be unchanged with ageing in man (Johnson et al 1986), as it was in comparisons between young and very old rats.

The D-xylose test has long been in clinical use for assessing intestinal absorptive functions, judged by changes in urinary excretion or plasma concentration of D-xylose after oral administration. Although some researchers had been aware that the potential changes in distribution or elimination need to be taken into account for accurate interpretation of data, it was only recently that pharmacokinetic evaluations using the D-xylose test were conducted in human studies, demonstrating an age-dependent decline in the renal clearance, explaining most of the age-dependent decrease in the renal excretion which was formerly considered to be suggestive of an age-dependent decline in the absorption (Schmucker 1985; Craig & Atkinson 1988). A simpler method for correcting for the declines in renal functions is to normalize the renal excretion after oral administration by that after intravenous administration (Kendall 1970). The same procedure was used to estimate the fractions absorbed of PEGs of various molecular weights by Donovan et al (1990) and Lin & Hayton (1983b). The present study demonstrated that the absorbed fractions estimated from urinary excretion by the corrected method were comparable with those estimated by pharmacokinetic model analysis and from faecal excretion, verifying the usefulness of the correcting method. Although we used the data at 24 h after administration for the comparison (Table 2), the collection period as short as 3 h appeared to give reliable estimates of the fraction absorbed. This can be explained by the fact that the collection period of 3 h is long enough compared with the elimination and absorption half-lives below 1 h, assuring that the elimination and absorption are almost completed within the period. In man, a generally used collection period of 5 h may be long enough to satisfy the conditions, as the absorption and elimination half-lives were reported to be 0·2–1 and 1–2 h, respectively (Johnson et al 1985, 1986). A shorter collection period may result in underestimates of the fraction absorbed, especially if absorption is not complete.

Although pharmacokinetic analysis predicted that the urinary excretion was almost completed by 3 h after intravenous administration (CL_r/CL_{tot} ratios were in agreement with the urinary recovery at 3 h), 10 to 20% of

additional urinary recovery was observed between 3 and 24 h in every age group. The predicted concentrations in plasma were slightly larger than the observed values at later times after intravenous administration. These observations suggest the involvement of a slower phase of elimination or the presence of minor radioactive metabolites. Thus, further studies may be required for more detailed description of D-xylose disposition, although this would not affect the estimates of the fraction absorbed on the basis of urinary excretion data as discussed in the preceding paragraph.

The suggestion of potential increases in the fraction absorbed with ageing would be of importance for poorly absorbed drugs for which oral absorption is incomplete. For those drugs, where the rate of absorption is likely to be restricted by intestinal absorption rather than by gastric emptying, the absorption rate constant might be also significantly affected, if the intestinal absorption (or membrane permeability) is changed with ageing. For highly absorbable drugs, where the extent of absorption is complete, and the rate of absorption is restricted by gastric emptying, the effects of age-dependent changes in gastric emptying, if any, on the absorption rate constant would be most significant. It is necessary to evaluate quantitatively the factors involved in oral absorption, gastric emptying, intestinal absorption (or membrane permeability) and intestinal transit, in relation to physicochemical properties or absorption characteristics of drugs to clarify age-dependent changes in the oral absorption.

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References

Craig, R. M., Atkinson A. J. (1988) D-Xylose testing: a review. Gastroenterology 95: 223–231

Donovan, M. D., Flynn, G. L., Amidon, G. L. (1990) Absorption of polyethylene glycols 600 through 2000: the molecular weight dependence of gastrointestinal and nasal absorption. Pharm. Res. 7: 863–867

Eberts, T. J., Sample, R. H. B., Glick, M. R., Ellis, G. H. (1979) A simplified, colorimetric micromethod for xylose in serum or urine, with phloroglucinol. Clin. Chem. 25: 1440–1443

Ferraris, R. P., Hsiao, J., Hernandez, R., Hirayama, B. (1993) Site density of mouse intestinal glucose transporters declines with age. Am. J. Physiol. 264: G285–G293

Freeman, H. J., Quamme, G. A. (1986) Age-related changes in sodium-dependent glucose transport in rat small intestine. Am. J. Physiol. 251: G208–G217

Gastaldi, G., Laforenza, U., Ferrari, G., Casasco, A., Rindi, G. (1992) Age-related thiamin transport by small intestinal microvillous vesicles of rat. Biochim. Biophys. Acta 1105: 271–277

Gentleman, J. F. (1986) New developments in statistical computing. Am. Statistician 40: 51–59

Johnson, S. L., Mayersohn, M., Conrad, K. A. (1985) Gastrointestinal absorption as a function of age: xylose absorption in healthy adults. Clin. Pharmacol. Ther. 38: 331–335

Johnson, S. L., Mayersohn, M., Conrad, K. A. (1986) Xylose disposition in humans as a function of age. Clin. Pharmacol. Ther. 39: 697–702

Kendall, M. J. (1970) The influence of age on the xylose absorption test. Gut 11: 498–501

Lin, C. F., Hayton, W. L. (1983a) GI motility and subepithelial blood flow in mature and senescent rats. Age 6: 46–51

Lin, C. F., Hayton, W. L. (1983b) Absorption of polyethylene glycol 400 administered orally to mature and senescent rats. Age 6: 52–56

Ma, T. Y., Hollander, D., Dadufalza, V., Krugliak, P. (1992) Effect of aging and caloric restriction on intestinal permeability. Exp. Gerontol. 27: 321–333

Mordenti, J. (1986) Man versus beast: pharmacokinetic scaling in mammals. J. Pharm. Sci. 75: 1028–1040

Ohkohchi, N., Himukai, M. (1984) Species difference in mechanisms of D-xylose absorption by the small intestine. Jpn. J. Physiol. 34: 669–677

Said, H. M., Hollander, D. (1984) Does aging affect the intestinal transport of 5-methyltetrahydrofolate? Digestion 30: 231–235

Schmucker, D. L. (1985) Aging and drug disposition: an update. Pharmacol. Rev. 30: 133–148

Thomson, A. B. R. (1979) Unstirred water layer and age-dependent changes in rabbit jejunal d-glucose transport. Am. J. Physiol. 236: E685–E691

Tsuji, A., Terasaki, T., Imaeda, N., Nishide, K., Nakashima, E. (1985) Effect of extracellular water volume on the distribution kinetics of β-lactam antibiotics as a function of age. J. Pharmacobiodyn. 8: 167–174

Vinardell, M. P. (1992) Age influences on amino acid intestinal transport. Comp. Biochem. Physiol. 103A: 169–171

Wagner, J. G. (1993) More complicated linear models. In: Pharmacokinetics for the Pharmaceutical Scientist. Technomic Publishing AG, Basel, pp 15–43

Weiner, R., Dietze, F., Laue, R. (1984) Age-dependent alterations of intestinal absorption. II. A clinical study using a modified D-xylose absorption test. Arch. Gerontol. Geriatr. 3: 97–108

Yuasa, H., Sekiya, M., Ozeki, S., Watanabe, J. (1994) Gastric emptying-limited oral absorption of α-linolenic acid administered as a milk fat-globule membrane (MFGM) emulsion in rats. Biol. Pharm. Bull. 17: 1262–1266