erster Linie für den Spezialisten bestimmt, sondern eher als Leitfaden für die zahlreichen «Gelegenheits-Pharmakokinetiker» gedacht. Zu einem solchen wird unversehens etwa der Chemiker, der sich um die Synthese neuer Chemotherapeutika, die vorwiegend in bestimmten Organen (ableitende Harnwege, Zentralnervensystem usw.) ihre Wirkung entfallen sollen, bemüht; oder der forensisch tätige Toxikologe, der sich vor die Frage gestellt sieht, in welchen Exkreten oder Gewebesäften der Nachweis eines bestimmten Pharmakons mit einer Methode definierter Empfindlichkeit und Spezifität am ehesten Erfolg haben kann. In diesen und ähnlichen Situationen werden einfache physikalisch-chemische Prinzipien, mit deren Hilfe eine erste Orientierung über das pharmakokinetische Verhalten wenig durchuntersuchter Verbindungen möglich ist, von recht grossem Nutzen sein.

Summary. Some correlations between the physico-chemical properties of drugs and their pharmacokinetic behaviour are outlined. Based on the permeability characteristics of simple model membranes (porous membrane, lipid membrane) permeation and distribution of drugs in the animal body can be described and understood on simple physico-chemical terms. Some clinically important aspects – the absorption of drugs from the intestinal tract, the passage through the blood-brain-barrier and the renal excretion as governed by passive tubular reabsorption – are discussed in more detail. Thereby it appears that the solubility of a drug in lipid material, which may be suitably expressed as partition coefficient between an organic solvent and a buffer solution of pH 7.4, is a major factor in determining its pharmacokinetic behaviour.

SPECIALIA

Physical Halflife of Radiochemically Pure (>99.9999%) ^{59}Fe and its MetabolicTurnover Rate in Man

Recent studies on the biological halflife and whole-body turnover rate of ^{59}Fe have shown that all commercial ^{59}Fe-preparations contain at least 1% contamination with ^{60}Co, ^{54}Mn and other radionuclides, so that the physical halflife of such impure ^{59}Fe-preparations starts to increase permanently after about 100 days (HEINRICH[1,2]). It was therefore necessary to prepare radiochemically pure ^{59}Fe and to investigate its physical halflife and metabolic turnover rate in man.

Anion exchange chromatography on Biorad-AG 1-X2 columns was used to separate ^{54}Mn, ^{134}Cs, ^{46}Sc, ^{60}Co, ^{65}Zn, etc., from commercial batches of ^{59}Fe which at delivery contained up to 1% of such radionuclide impurities. The ^{59}Fe was eluted from the strongly basic anion exchange resin with 3N HCl. Analytical anion exchange chromatography, thin layer and paper chromatography with 3 different solvent systems as well as γ-spectroscopy demonstrated a radiochemical purity of >99.9999% for the purified ^{59}Fe (HEINRICH and GABBE[3], HEINRICH[4]).

A total of 16 separate ^{59}Fe-standards were prepared from 5 different batches of radiochemically pure ^{59}Fe and measured directly for radioactive decay in a NaI-crystal well detector and within the 4π-geometry of a small detector with liquid organic scintillator. Data from both detectors were corrected for constant over-all efficiencies of $\pm 0.1\%$ and $\pm 0.4\%$ respectively. The decay constant λ was calculated from all measurements of the 16 or 9 ^{59}Fe-standards regarding the single decay rates to scatter around on a single regression line. Identical results were obtained with both detectors (Table I) and differed significantly from the published and presently used values for the decay constant or physical halflife of ^{59}Fe (Table II). The considerable variation in the published values for the physical halflife of ^{59}Fe (45 days[5]; Documenta Geigy Scientific Tables[6]; 45.6 days, PIERROUX et al.[7]; LEDERER[8]; and even 47 days, WAHL[9]; STROMINGER[10]) may be explained by a different age and therefore different contamination of the ^{59}Fe-preparations used with ^{60}Co, ^{54}Mn, ^{65}Zn, ^{46}Sc, ^{134}Cs, etc. In addition these authors performed their direct ^{59}Fe decay measurements mostly

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Table I. Decay constant (λ) and physical halflife ($T_{1/2p}$) of radiochemically pure (> 99.9999%) ^{59}Fe calculated from radioactive decay measurements with NaI-crystal-well and liquid organic scintillation detectors

Scintillation well detector	No. of ^{59}Fe-samples	Decay measurement Period (d)	Points	Decay constant (d^{-1}) λ	$\pm$ S.E.	Physical halflife (days) $T_{1/2p}$	$\pm$ S.E.
NaI-crystal	16	259–506	8–19	0.015568	0.0000056	44.52	0.016
Liquid organic	9	239–402	7–13	0.015564	0.0000092	44.53	0.026

S.E. = Standard error.

Table II. Biological halflife and turnover rate of whole-body Fe-pool in males and females as calculated from the whole-body measurements of the effective halflife ($T_{1/2e}$) of ^{59}Fe and the physical halflife ($T_{1/2p}$) of radiochemically pure (> 99.9999%) ^{59}Fe and the presently still accepted literature values for $T_{1/2p}$ of ^{59}Fe

		Males (70 kg)			Menstruating females (60 kg)		
Iron content (mg/kg)		55			45		
Whole-body iron pool (mg)		3850			2700		
Effective ($T_{1/2e}$)[a] ^{59}Fe halflife (days)		43.6			43.1		
Physical ($T_{1/2p}$) ^{59}Fe halflife (days)		44.52[b]	45.0[c]	45.6[d]	44.52[b]	45.0[c]	45.6[d]
Biological ($T_{1/2b}$)[e] ^{59}Fe halflife (days)		2190	1430	1010	1340	1020	783
Turnover rate of wholebody iron pool:	(%/day)	0.032	0.048	0.069	0.052	0.068	0.089
	(mg Fe/day)	1.22	1.86	2.64	1.39	1.84	2.39

[a] $T_{1/2e}$ of absorbed ^{59}Fe was measured in the ^{137}Cs-free ^{59}Fe energy channel of a 4π whole-body radioactivity detector with liquid organic scintillator (HEINRICH et al.[11]) over at least 1 year (HEINRICH[1]). [b] $T_{1/2p}$ of radiochemically pure (> 99.9999) ^{59}Fe (our measurements). [c] $T_{1/2p}$ of ^{59}Fe according to 3rd edn. Intern. Direct. Radioisotopes, I.A.E.A., Vienna 1964[5]. [d] $T_{1/2p}$ of ^{59}Fe according to 6th edn. *Table of Isotopes*[8]. [e] $T_{1/2b}$ as calculated from $T_{1/2e} = (T_{1/2p} \times T_{1/2b}/T_{1/2p} + T_{1/2b})$ [1].

over only 2–3 physical halflife periods (~89–134 days) when the permanent increase of the physical ^{59}Fe halflife just becomes evident. In contrast to the available commercial ^{59}Fe-preparations with only 99% radiochemical purity (only at delivery), the physical halflife of 99.9999% pure ^{59}Fe remains constant up to the 506th day.

The effective halflife of retained radiochemically pure ^{59}Fe was measured in males and menstruating females with normal iron stores within the 4π-geometry of a wholebody radioactivity detector (HEINRICH et al.[11]). The biological halflives and turnover rates of the whole-body iron pool (Table II) were calculated from the effective halflives of ^{59}Fe (Table II) and the correct physical halflife of radiochemically pure ^{59}Fe (Table I) using formula [1] (Table II). It is evident from the data in Table II that the use of the presently recommended physical halflife of 45.6 days for ^{59}Fe results in a biological halflife which is shorter by a factor of 2, and a wholebody turnover rate which is twice as high if compared with the corresponding data calculated from the measured effective halflife ($T_{1/2e}$) and using the physical halflife of 44.52 days for the radiochemically pure (> 99.9999%) ^{59}Fe (Table II). The fact that all published wholebody counter studies on the biological halflife and turnover rate of the wholebody iron pool in man were performed with test doses and standards of unpurified ^{59}Fe (= 99% original radiochemical purity) is a possible explanation for the described unrealistic high turnover-rate values of 0.14–0.31%/d (= 6–13 mg Fe/d for a 4.2 g Fe-pool), which are 5–10 times as high as the commonly accepted values for the iron requirement of man (~1.2 mg/day) (HEINRICH[4]). The whole-body iron turnover rates which were calculated from the measured physical and effective half-lives of absorbed radiochemically pure ^{59}Fe (Tables I and II) indicate a daily iron turnover or requirement of about 1.2 mg in males and 1.4 mg in females.

Zusammenfassung. Erstmalig wurde radiochemisch reines ^{59}Fe (> 99,9999%) eingesetztg, um die radioaktive Halbwertzeit des ^{59}Fe mit 44,52 $\pm$ 0,016 ($\overline{m}_a \pm$ SE) Tagen entsprechend einer Umwandlungskonstanten λ = 0.015568 $\pm$ 0.000 0056 [d^{-1}] zu bestimmen. Radiochemisch reines ^{59}Fe wird im menschlichen Körper bei Männern mit einer Umsatzrate von 0,032%/Tag (= 1,2 mg Fe/Tag) und bei menstruierenden Frauen mit 0,052%/Tag (=1,4 mg Fe/Tag) ausgeschieden. Diese Gesamtkörper-^{59}Fe-Eliminationsrate entspricht dem Eisenbedarf des Menschen.

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