Observation

MARGINS OF SAFETY OF INTRAVASCULAR CONTRAST MEDIA: BODY WEIGHT, SURFACE AREA OR TOXICOKINETIC APPROACH?*

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Received in June 2004

The margin of safety of a drug is defined as the ratio between toxicity in animals and safety in humans. For intravascular contrast media, the margin of safety is traditionally the ratio between LD_{50} and diagnostic dose, both doses being based on bodyweight. The shift to surface area dramatically reduces this margin to unacceptable values. Toxicokinetics, which relates systemic exposure associated with early toxic signs in animals to plasma level in man, seems the most accurate and predictive criterion.

KEY WORDS: *acute toxicity, diagnostic dose, LD_{50}, toxicokinetics*

Efficacy and safety are the two clinically relevant characteristics of every drug. Safety, indeed, is not an absolute value, but is rather a measure of the distance between the therapeutic dose and the toxic dose of the drug. Thus, toxic doses assessed from pre-clinical studies are compared with the dose expected for therapy and the ratio between these doses is called margin of safety (MS). The greater the ratio, the greater the safety (clinical manageability) of the drug.

Intravascular contrast agents are characterized by no metabolism, fast excretion and relative biological inertness. These favourable properties, coupled with their single use in clinical practice, allow that MS is simply calculated as the ratio between the end point of single-dose toxicity in animals and the diagnostic dose in humans. Differences in animal toxicity, expressed as LD_{50}, based on body weight have been shown to predict different human tolerability of iodinated contrast media (1, 2).

Transformation of lethality data from body weight to surface area is recommended by Food and Drug Administration (FDA) for oncologic drugs, but the same approach has also been applied to other injectables.

Toxicokinetics, i.e. the determination of drug plasma level at nearly toxic doses is also a regulatory request to associate systemic exposure in animals with threshold doses for tolerability (3, 4).

The objective of this paper was to compare the three approaches and assess their predictability for human safety of iodinated and paramagnetic contrast media.

METHODS

MS for ionic and non-ionic iodinated contrast media (CM) as well as paramagnetic CM were calculated according to LD_{50} values based on body weight or transformed to surface area or as a ratio between maximal plasma levels (C_{max}). Intravenous LD_{50} values in mice were obtained from in-house historical data or from literature. Standard data for animal and human surface areas were as follows: for

* Partly presented at the 3rd Croatian Congress of Toxicology, Plitvice, Croatia, 26-29 May 2004

Table 1 *Iodinated contrast media. LD_{50}-based margins of safety (MS): body weight (BW) and surface area (SA) approaches. Values in mice*

	Contrast agent	$\frac{LD_{50}}{g\ kg^{-1}}$	MS (BW)	$\frac{LD_{50}}{mg\ cm^{-2}}$	MS (SA)
I generation	Sodium iodide	0.9*	4.5	0.5	0.8
	Uroselectan	2.9*	14.5	1.7	2.5
	Methiodal	2.5*	12.5	1.5	2.2
	Uroselectan B	3.7	18.5	1.0	1.5
	Iodopyracet	2.8	14.0	0.8	1.1
II generation	Acetrizoate	6.2	7.8	1.7	0.6
	Diatrizoate	7.2	9.0	2.0	0.7
	Iothalamate	8.0	10.0	2.2	0.8
	Iodamide	8.0	10.0	2.2	0.8
	Iocarmate	5.5	6.9	1.5	0.6
	Ioxaglate	10.0	12.5	2.7	1.0
III generation	Metrizamide	18.1	22.6	4.9	1.8
	Iopamidol	21.8	27.3	5.9	2.2
	Iohexol	18.4	23.0	5.0	1.9
	Iopromide	18.5	20.6	4.5	1.7
	Iomeprol	19.9	24.9	5.4	2.0
	Iodixanol	21.9	27.4	5.9	2.2
	Iotrolan	22.6	27.9	6.1	2.3

** no data available for the mouse, rat data reported.*

a 50 kg man surface area was set at 15000 cm^2; for a 200 g rat surface area was set at 342 cm^2; for a 20 g mouse surface area was set at 73.7 cm^2 (5).

C_{max} values were obtained from in-house or contract laboratory studies conducted by intravenous route in different animal species.

Human doses used for the calculation were as follows: iodinated CM 10 g (iodine) per person for CM of the first generation or 0.7 mg cm^{-2}, 40 g per person for CM of the second and third generation or 2.7 mg cm^{-2} (1); paramagnetic CM: 0.1 mmol kg^{-1}.

RESULTS

LD_{50} approach

When doses are expressed in terms of body weight, the margins of safety for ionic contrast media range between 7 and 12. For non-ionic contrast media, the margin of safety is between 18 and 28. When paramagnetic contrast media are considered, the LD_{50} to diagnostic dose ratio is even greater, leading to a factor of 100 and more.

Body surface area approach

New concepts in safety evaluation, endorsed by regulatory authorities, suggest the surface area as a more suitable parameter than body weight to express the given dose. The surface area criterion assumes that body area more properly represents the area where drugs distribute, independently on the weight of the organism. This approach was originally developed for drugs with pharmacological and toxicological properties far different from those of contrast media, e.g. anticancer agents. As can be seen from Table 1, the transformation to surface area leads the second generation of iodinated CM to result in paradoxical ratios between lethal doses and the clinical dose. For example, diatrizoate would be administered to patients at a dose corresponding to 1.3 times the dose which is lethal for 50 % of animals. Although this ratio is substantially better with iodinated CM of the third generation (low-osmolar non ionics), a MS of about 2 is obviously insufficient to guarantee a safe clinical use of all compounds here listed. In addition, considering clinical applications for which the standard dose is sometimes exceeded (e.g. angiography) this ratio falls to 1 or even below, thus coming back to the situation of ionics.

Paramagnetic CM remain safer in animals than iodinated CM, even after transformation to surface area (Table 2).

Toxicokinetics approach

Toxicokinetics is a non-lethal method, which, among other pharmacokinetic parameters, determines the maximal plasma concentration (C_{max}) obtained after the administration of the Maximum Tolerated

Table 2 *Paramagnetic contrast media. LD_{50}-based margins of safety: body weight (BW) and surface area (SA) approach.*

Contrast Medium	LD_{50} (mice)		Effective dose (man)		Margin of Safety	
	mmol kg^{-1}	μmol cm^{-2}	mmol kg^{-1}	μmol cm^{-2}	BW	SA
MultiHance®	6	3.5	0.05	0.165	120	21.2
Magnevist®	6	3.5	0.1	0.33	60	10.6
ProHance®	14	8.2	0.1	0.33	140	24.8

Data for animal and human surface areas were taken from literature and standardized as follows: man = 50 kg, 15000 cm^2 surface area; rat = 200 g, 342 cm^2 surface area (5).

Dose (MTD). The margin of safety is calculated by the ratio C_{max} animal MTD/C_{max} human clinical dose, thus providing comparison between actual systemic exposure. Margins of safety calculated as described above are about 5 and 30 for Iomeron® and MultiHance®, respectively. Data for Iomeron® and MultiHance®, taken as representative of non-ionic iodinated CM and paramagnetic CM are shown in Tables 2 and 3.

Table 3 *Toxicokinetic approach*

Contrast Medium	Cmax at clinical dose*	Cmax at MTD					
		Rat		Dog		Monkey	
		value	ratio	value	ratio	value	ratio
Iomeron®/ mg mL^{-1}	6.5	≈ 32	5	≈ 27	4	NA	
MultiHance®/ mmol mL^{-1}	0.9	20	22	NA		32	36

** Iomeron® clinical dose: 200 mL of Iomeron 400 per man (1)*
MultiHance® clinical dose: 0.1 mmol kg^{-1} (reported in the manufacturer's package insert)
NA: Not Available

DISCUSSION

Extrapolation of safety data from animals to man is often difficult due to differences in metabolism and physiology among mammal species. Although in regulatory perspective contrast media are considered as drugs, the absence of metabolism, free distribution to body fluids and the predominant renal excretion make the extrapolation somewhat easier in respect to true drugs.

In view of the single use of contrast media in patients, data from single doses in animals are most suitable for the evaluation of margins of safety.

The traditional approach based on LD_{50} value has shown differences in toxicity between classes of iodinated contrast media (1) and between compounds of the same class (2). This approach however has two limitations. The first is practical; LD_{50} test is no longer allowed by health authorities (6), rendering unavailable comparison for newly developed contrast media. The second is conceptual; the ratio between a lethal dose in animals and a diagnostic dose in humans will furnish margins of safety in terms of lethality, but not in terms of tolerability. Transformation to surface area substantially decreases this ratio to unacceptable, unrealistic values, when compared to clinical occurrence of severe adverse reactions (7). Moreover, the cautionary approach to select endpoints at lower doses (e.g. MTD, NOAEL, NOEL) further decreases the margins of safety below the unit.

In contrast, at these doses toxicokinetics can assess actual systemic exposure when the limits of tolerability are reached. The ratio between these parameters, in particular C_{max}, and the anticipated human plasma levels are thought to provide a more accurate estimation of the margin of safety.

Interestingly, the higher ratio demonstrated by MultiHance® (paramagnetic CM) versus Iomeron® (iodinated CM) corresponds to greater clinical tolerability of MRI CM in respect to iodinated ones (8-10). The use of the toxicokinetic approach is thus recommended for a reliable assessment of margins of safety.

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Sažetak

GRANICA SIGURNOSTI ZA INTRAVASKULARNA KONTRASTNA SREDSTVA: TJELESNA TEŽINA, POVRŠINA ILI TOKSIKOKINETIČKI PRISTUP?

Granica sigurnosti lijeka određena je kao odnos između toksičnosti u životinja i sigurnosti za čovjeka. Za intravaskularna kontrastna sredstva granica sigurnosti je poznati odnos između LD_{50} vrijednosti i dijagnostičke doze, gdje su obje doze temeljene na tjelesnoj težini. Transformacija vrijednosti na površinu značajno smanjuje granicu sigurnosti do neprihvatljivih vrijednosti. Toksikokinetika, koja povezuje sistemsko izlaganje povezano sa ranim znakovima toksičnosti u životinja i s količinama u plazmi čovjeka, čini se, najtočniji je i najpredvidljiviji kriterij.

KLJUČNE RIJEČI: *akutna toksičnost, dijagnostička doza, LD_{50}, toksikokinetika*

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