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Pharmacochemical Profile of Iopromide

Wolfgang Muetzel¹ and Ulrich Speck¹

Iopromide (Schering, Berlin) is a new nonionic, monomeric contrast medium containing three different substituents on the triiodinated benzene ring. Iopromide exhibits low osmolality and viscosity in aqueous solutions of high concentrations. It has been shown to have a remarkably low intravenous toxicity in mice and rats. Neural tolerance was found to be equal to or better than that of metrizamide when injected in rats intracisternally and intracerebrally, respectively. The effects of iopromide after selective peripheral and cerebral arterial injections in rats were demonstrated to be very moderate at high dosages. The interaction of iopromide with proteins and membranes was found to be considerably low due to its hydrophilicity. Excretion of iopromide is fast and predominantly by the renal route. On the basis of the preclinical profile iopromide is a very promising contrast agent, being most suitable for all angiographic indications, including digital subtraction angiography, urography, and computed tomography.

Iopromide, which is the proposed international nonproprietary name for 5-methoxyacetyl-amino-2,4,6-triiodoisophthalamide acid-[(2,3-dihydroxy-N-methylpropyl)-(R,S-2,3-dihydroxypropyl)]-diamide, was synthesized in 1978 in the research laboratories of Schering, Berlin [1] (fig. 1). Iopromide is being developed for use in angiography, urography, and computed tomography (CT) [2]. In order to define the margins of safety afforded by the new nonionic, water-soluble contrast agent when employed in human clinical use, the compound was subjected to a number of physicochemical, pharmacologic, toxicologic, and pharmacokinetic experiments as well as to several biochemical tests. The experiments were designed to reveal qualitative and quantitative aspects of toxic effects by comparing iopromide with metrizamide and iopamidol.

Materials and Methods

Contrast Media

Iopromide was used as a sterile, aqueous solution containing 300 or 370 mg I/ml (Schering, Berlin). Metrizamide was in the form of the lyophilized substance (Nyegaard, Oslo), which was dissolved in the required concentration with 5 mg sodium bicarbonate/100 ml solution immediately before the experiments. Iopamidol too was in the form of a sterile, aqueous solution containing 300 or 370 mg I/ml (Bracco, Milan).

The osmotic pressure and viscosity were measured at 37°C by vapor-pressure osmometry and capillary viscosimetry, respectively. The distribution coefficient was determined in a mixture of 1-butanol/Tris-HCl buffer, pH 7.6, at room temperature.

Tolerance Studies

The acute general tolerance (LD₅₀) in male and female mice (NMRI strain, 18–22 g) and rats (Wistar, 90–100 g) was investigated by injecting the contrast media solutions (300 mg I/ml) once in varying volumes at a rate of 2 ml/min into a lateral tail vein. Six animals per dose were observed for 7 days.

The tolerance after intracerebral administration in the rat was tested according to the method of Valzelli [3], modified as described [4]. The acute neural tolerance was investigated by single injections of the contrast material into the cisterna cerebello-medullaris and into the carotid artery, respectively, of nonanesthetized rats (Wistar) according to [4]. The intensity of vessel pain after intraarterial (a. femoralis) injections was tested in rats (Sprague-Dawley) as described [5].

Biochemical Pharmacology

The morphologic changes of human red blood cells when mixed with the contrast media in several proportions were observed under a light microscope according to [6]. The binding of contrast media to human plasma proteins was determined by equilibrium dialysis [7].

The influence of the contrast media on the complement system of human serum was investigated by observation of complement-mediated inhibition of the hemolysis of antibody-coated sheep erythrocytes and the activation of total complement by determination of CH₅₀ values [8].

The inhibition of lysozyme by the contrast material was tested according to [9] and the liberation of histamine from mast cells of rats according to [8].

Pharmacokinetics

The ¹²⁵I-labeled contrast media were intravenously injected once into male rats at a dose of 60 mg I/kg. In order to establish the main route of excretion, biliary and urinary radioactivities were measured up to 3 hr after injection (10 animals, respectively, acute biliary fistulae in one group).

Results

The data of all calculations, observations, and measurements are compiled in table 1. Aqueous solutions of iopromide and iopamidol exhibit osmotic pressures that are somewhat higher than those of metrizamide at corresponding concentrations. Inversely, the viscosity of iopromide—and iopamidol—formulations is lower than that of

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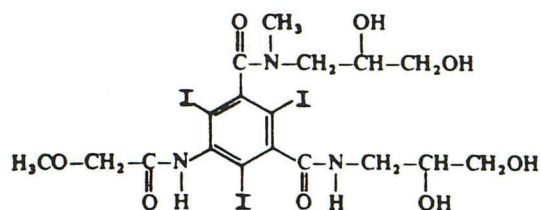


Fig. 1.—Chemical structure of iopromide.

corresponding solutions of metrizamide. Both observations can be related to the degree of association of the molecules in water. Iopromide like iopamidol obviously forms fewer associates than metrizamide when dissolved in water.

Iopromide and iopamidol are much more hydrophilic than metrizamide, as indicated by their partition coefficients. The distribution of OH-functions on substituents of the triiodinated benzene ring is more even in the structures of iopromide and iopamidol than of metrizamide which only has one part containing OH-groups (glucosamine).

The correlation between hydrophilicity and toxicity of homologous contrast media was recognized very early [10]. In general, the most hydrophilic compounds are tolerated best. Therefore, it is not surprising that iopromide and iopamidol are better tolerated than metrizamide in rats and mice, as this is evident from LD₅₀s after intravenous injections.

The neural tolerance of iopromide after intracerebral injection into the rat's brain was better than that of metrizamide, and very much the same after intracisternal injection. Iopamidol, which was tested concurrently in both studies, was tolerated better than metrizamide and iopromide.

After intracarotid injections of iopromide into rats only behavioral anomalies, but no cramps or convulsions, were observed in 50% of the animals at a dose of 3 g iodine/kg. Similar symptoms were observed when metrizamide and iopamidol were injected at a dose of 2 g I/kg.

Iopromide, metrizamide, and iopamidol were tolerated painlessly when injected at concentrations of 300 mg I/ml into the femoral artery of the rat. With concentrations of 370 mg I/ml no pain was observed in 10 animals using metrizamide, while iopromide and iopamidol were painful in one or two of 10 animals, probably due to the relative hypertonicity of the solutions compared with metrizamide.

After incubation of human blood with metrizamide the shape of erythrocytes changed markedly (e.g., echinocytes, spherocytes), occurring significantly ($p < 0.01$) more frequently than in mixtures containing iopromide or iopamidol. If the effect of metrizamide on erythrocytes is taken as 1, then the relative effect of iopromide and iopamidol is 0.15.

In the concentration of 1.2 mg I/ml binding of iopromide to the protein of human plasma was 0.9%, that of metrizamide 4.3%, and that of iopamidol 2.9%.

With regard to complement-mediated inhibition of hemolysis, iopromide exhibited a mean effective concentration of 15 mg I/ml, metrizamide and iopamidol of 11 and 12 mg I/ml, respectively. Dose-dependent activation of the complement system in human serum by iopromide, metrizamide, and iopamidol led to the following result:

Under the reaction conditions at an iopromide concentration of 176 mg I/ml, a metrizamide concentration of 101 mg I/ml, and an iopamidol concentration of 190 mg I/ml, 50% of the activity of the used complement remained. If the hypothesis first proposed by Lasser et al. [11] is followed, that activation of the complement by contrast media is correlated to some of their side effects, iopromide

TABLE 1: Preclinical Characteristics of Iopromide, Metrizamide, and Iopamidol, Three Monomeric Nonionic Contrast Media

	Iopromide	Metrizamide	Iopamidol
Physical properties:			
Molecular weight	791	789	777
Iodine (%)	48.1	48.2	49.0
Osmolality (37°C), aqueous solution:			
300 mg I/ml (mmol · kg ⁻¹ H ₂ O)	607	485	619
370 mg I/ml (mmol · kg ⁻¹ H ₂ O)	792	571	800
Viscosity (37°C), aqueous solution:			
300 mg I/ml (centipoise)*	4.8	6.2	4.5
370 mg I/ml (centipoise)	9.6	15.2	9.5
Partition coefficient (1-butanol/buffer, pH 7.6)	0.14	0.37	0.11
Tolerance:			
LD ₅₀ , mouse, intravenous (g I/kg)	16.5	12.1	16.4
LD ₅₀ , rat, intravenous (g I/kg)	11.4	10.3	11.3
ED ₅₀ , rat, intracerebral (mg I/kg)	86	53	154
ED ₅₀ , rat, intracisternal (mg I/kg)	53	52	127
ED ₅₀ , rat, arteria carotis (g I/kg)	3.0	2.0	2.0
ED ₅₀ , rat, arteria femoralis (g I/kg)	>3.8	>3.8	>3.8
Biochemical pharmacology:			
Erythrocyte morphology (relative activity of metrizamide = 1.0)	0.15	1.0	0.15
Protein binding (% bound)	0.9	4.3	2.9
I ₅₀ , hemolysis inhibition (mg I/ml)	15	11	12
I ₅₀ , complement activation (mg I/ml)	176	101	190
I ₅₀ , inhibition of lysozyme (mg I/ml)	142	132	157
Histamine release from mast cells (% release at 150 mg I/ml)	7	25	17
Pharmacokinetics in rat after intravenous injection:			
Excretion via the urine (% of dose in 3 hr)	82	86	87
Excretion via the bile (% of dose in 3 hr)	6	7	2
Renal elimination half-life (min)	16	19	19

* 1 poise = 10⁻¹ Pa.s (SI unit).

and iopamidol should cause fewer side effects clinically than metrizamide, which is very well tolerated.

Differences with respect to their property of inhibiting lysozyme, which altogether correspond to the partition coefficients, were yielded for the three contrast media tested. Again, nonspecific binding of lipophilic regions of the molecules to hydrophobic regions in the enzymes may be assumed to be a force determining the interaction. The property of the contrast media tested of liberating histamine from rat peritoneal mast cells might have a direct relationship to their protein binding. Iopromide exhibited less influence than metrizamide and iopamidol at the high concentration tested. On the basis of clinical observations that histamine liberation from mast cells is related to anaphylactoid reactions, these side effects

can be expected more rarely using iopromide compared with metrizamide or iopamidol.

More than 80% of the dose of ^{125}I -labelled contrast media was excreted via the kidneys within 3 hr after intravenous injection of 60 mg I/kg body weight into male rats. The renal elimination half-life for iopromide was calculated to be 16 min, for metrizamide and iopamidol 19 min. Two per cent of the dose was excreted via the bile using iopamidol, 6% and 7%, respectively, using iopromide or metrizamide.

The three contrast media observed revealed pharmacokinetic characteristics showing them to be basically suitable as contrast media for urography.

Discussion

It is concluded from the preclinical profile of iopromide that the new nonionic contrast agent shows properties predicting a broad margin of safety when employed in clinical use. Chemotoxic reactions following the intravascular injection of high concentrations of iopromide as well as systemic, anaphylactoid reactions may occur less often than with conventional contrast agents and metrizamide. Iopromide should be most suitable as a contrast medium for all angiographic indications, including digital subtraction angiography, urography, and for contrast enhancement in CT.

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