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Contrast Media as Histamine Liberators in Man

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Abstract

6 minutes after Joduron® 70% (0.5 ml/kg), Biligrafin® 30% (0.4 ml/kg), Urografin® 60% (0.5 ml/kg), Urovison® 58% (0.5 ml/kg), Urovist® 65% (0.75 ml/kg) and Conray® 70% (0.5 ml/kg) (within 1 minute injected) the level of circulating histamine in plasma is increased from less than 1.0 ng/ml to 2.0–2.5 ng/ml. The elevated levels return to normal within 20 minutes, in the case of Joduron® 70% and Biligrafin® 30% slower than after the other contrast media. Urivison® 30%, infused over 4 minutes (total dose 4 ml/kg), as dextrose 50%-solution (0.5 ml/kg) failed to change histamine concentration in plasma. Obviously the histamine liberating effect of the contrast media is a specific effect of these agents.

Introduction

Since the introduction of the first positive contrast media into clinical practice [52] disturbing side effects of these agents are a still unsolved problem. There is no doubt that the modern threefold iodinated derivatives of benzene have led to a decrease of unwanted reactions in the course of application of contrast media [25, 43, 70 81] but still now as in earlier times death may occur in connection with their application for clarifying diagnostic problems [56–58].

Obviously the basic mechanisms by which even preparations of modern contrast media may bring about their unwanted effects are of different origins, for instance chemotoxic, allergic or idiosyncratic; possibly these preparations cause unwanted effects by their hypertonic nature [26, 29, 41, 56, 71]. Because allergic or idiosyncratic symptoms can partly be imitated by the injection of histamine [38] liberation of this amine may cause allergic or idiosyncratic incidents in connection with the application of contrast media. The liberation of histamine, as the main reason for anaphylactic reactions in connection with the usage of different drugs, measured by reliable methods is shown only for a few of them. A regular increase of plasma histamine levels without severe clinical consequences could be ascertained for some more [33, 35, 38, 45].

For most drugs the elevation of plasma histamine especially during anaphylaxis has to be shown in future, although a large variety of them are thought to be powerful liberators of histamine [4, 53, 54]. Liberation of histamine by contrast media was discussed already by MANN [40]. OLSSON [51] and OCHSNER et al. [48] supposed to inhibit unwanted reactions after injections of contrast media by using antihistaminic drugs preliminary. Later on OCHSNER and CALONJE [49] even did not believe in that anymore.

ROCKOFF et al. [64, 65] showed that different contrast media of the threefold iodinated type caused histamine liberation from peritoneal mast cells of rats. But they used rather high concentrations: 5–40% (w/v). The authors themselves concluded that 'the role of histamine release in their clinical toxicity has not been established'.

PETERS et al. [59] could not find a regular liberation of histamine by contrast media. But in the light of modern methodology their results are equivocal. LASSER et al. [30] could not 'find any evidence of histamine release' 'in experiments with dogs' published in a very short abstract. An elevation of histamine levels in

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local venous blood was observed after the injection of contrast media into the adjacent artery [31]. BRASCH et al. [2] injecting 'slowly by hand' '50 to 100 ml of intravenous 60% meglumine iothalamate (Conray)', and Rockoff and Aker [66] injecting 20–60 ml of 75% Hypaque® (20–34 ml/min) into the pulmonary artery or right heart failed to induce a constant liberation of histamine.

The question seems still open, if contrast media when injected according to clinical use cause an increase of plasma levels of histamine. Therefore levels of histamine in venous blood were estimated after i.v. injection of diodonemorpholine (Joduron® 70%), iodipamide (Biligrafin® 30%), diatrizoate (Urografin® 60%, Urovison® 30% and 58%, Urovist® 65%) and iothalamate (Conray® 70%) given in doses recommended for clinical use.

Methods

(1) Run of experiments

This study was carried out in male healthy volunteers, aged between 20–30 years, who – as far as known – did not suffer from allergic diseases and did not get contrast media previously. So there was no special risk applying contrast media [42].

Prior to the application of a special contrast medium 30 ml of blood were drawn through a plastic cannula (Braunüle® No. 1) from a right anticubital vein into Liquemin® moistened plastic syringes without the use of a tourniquet. Then the contrast medium was injected into a contralateral vein. The injection time was 1 minute starting at 0. Only Urovison® 30% was infused during 7 minutes. 3, 6, 10, 20 and 30 or 40 minutes after start blood samples were drawn from the right side-vein.

(2) Substances and materials

Ion exchange material: Dowex 50 WX 4, 100–200 mesh, Serva (Heidelberg), No. of article: 41561. Preparation as described by MEYER-BURGDORFF et al. [46]; storage in prepared state no longer than 2 weeks in a 4 °C refrigerator.

Liquemin®: Hoffmann-La Roche, 5000 USP-U/ml.

o-Phthaldialdehyde: Calbiochem (Luzern, Switzerland), No. of article: 5261. Solution: 5 mg/ml methanol, use only of fresh prepared solution.

Silicone solution: Siliconlösung Serva pract., Serva (Heidelberg), No. of article: 35130.

Water: Aqua demin. Twice destilled in a quartz-destiller.

Other reagents of p.a. grade: Merck (Darmstadt).

Intravenously applicated preparations:

Diodonemorpholine: Joduron® 70%, Cilag (Schaffhausen).

Iodipamide: Biligrafin® 30%, Schering (Berlin).

Diatrizoate: Urografin® 60%, Urovison® 30% and 58%, Urovist® 65%, Schering (Berlin).

Iothalamate: Conray® 70%, Byk-Gulden (Konstanz).

Dextrose 50%: T50, Schi-Wa (Glandorf).

The blood samples were injected into iced glass vessels, which, like all other glass ware utilized after rinsing with the a.m. water preparations, were twice siliconized to avoid loss of histamine by absorption [63].

(3) Estimation of histamine

Estimation of free histamine in plasma from the different blood samples was carried out according to LORENZ et al. [34, 37, 39] after the blood was rotated at 4 °C for 60 minutes with 1000 *g*. Essentially the procedure consists of two steps: binding of histamine on cation exchange material and extraction with butanol [73]. Finally histamine was measured after coupling with phthaldialdehyde with the aid of fluorometric measurement using a Fluorispec (fluorescence spectrophotometer, model SF-1, Baird-Atomic). The procedure was calibrated with synthetic histamine, added to identical plasma samples from a big pool. Values are given as mean ± S.E.M.

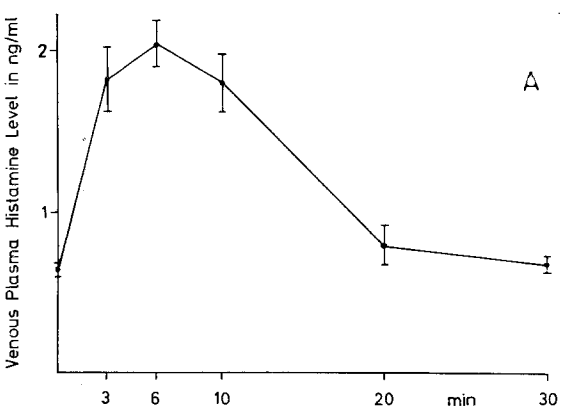
Results

(1) Normal plasma concentrations of histamine

The average starting concentration of plasma histamine was found to be 0.84 ± 0.03 ng/ml (n = 40, range 0.6–1.4 ng/ml).

(2) Liberation of histamine by Joduron® 70%

Figure 1A shows the course of histamine levels after injection of diodonemorpholine (Joduron® 70%). At that time when the contrast



A 0.5 ml/kg diodonemorpholine (Joduron® 70%) (n = 5),

medium was used it was recommended to take 20–40 ml of the preparation for an adult patient depending on his body weight. Therefore our 5 volunteers received Joduron® 70% in a dose of

0.5 ml/kg. Already 3 minutes after the start of injection the level of free histamine in plasma was significantly increased from 0.64 ± 0.04 ng/ml to nearly thrice of the starting value: 1.82 ± 0.20 ng/ml ($p<0.0005$).

Until 10 minutes after injection the histamine level remained elevated with just a little higher maximum after 6 minutes: 2.04 ± 0.14 ng/ml.

20 minutes after the injection the level of free histamine had returned almost to the starting value.

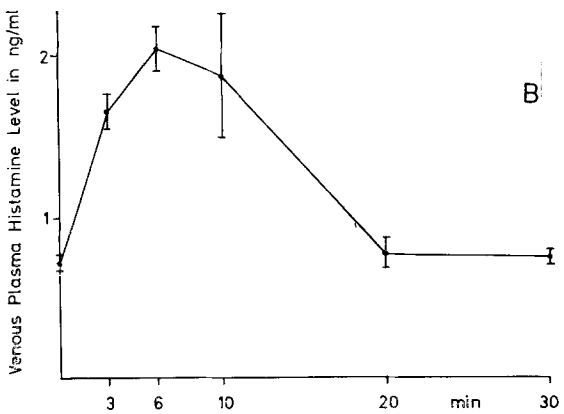
All volunteers complained about unpleasant side effects; as heat feeling (prob. 1–5), urticaria (prob. 4), dizzyness sand pain along the vein used for injection (prob. 5).

(3) Liberation of histamine by Biligrafin® 30%

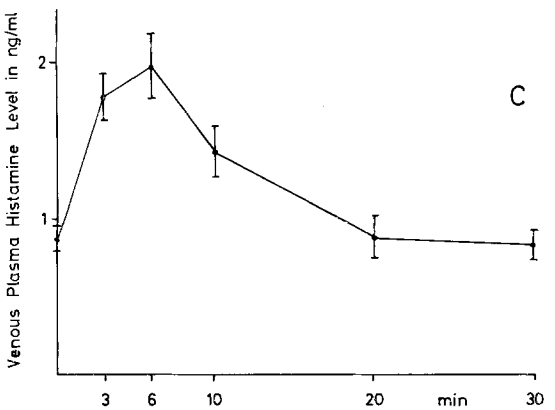
Biligrafin® 30% was injected in a dose of 0.4 ml/kg. The dose again corresponds to the recommendation of the manufacturer. Obviously histamine was liberated by Biligrafin® 30% in a similar manner as by Joduron® 70% (Fig. 1B). In 5 volunteers the average levels significantly increased from 0.72 ± 0.05 ng/ml to 1.66 ± 0.11 ng/ml 3 minutes after injection ($p < 0.0005$) and remained high until 10 minutes. Again a maximum value was found 6 minutes after injection: 2.04 ± 0.14 ng/ml. 4 persons complained of side effects as heat feeling (prob. 1 and 2), vomitus (prob. 2), epigastric pain (prob. 4) and nausea (prob. 5).

(4) Liberation of histamine by Urografin® 60%

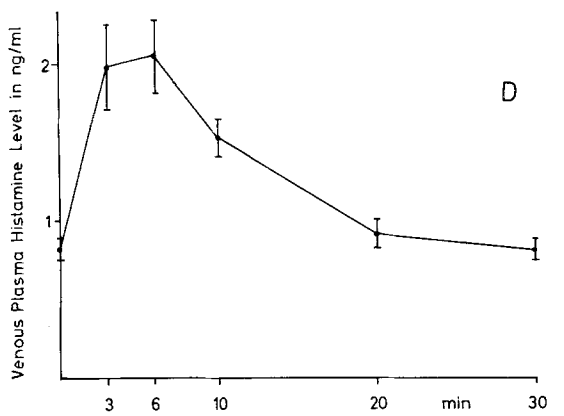
As with Joduron® 70% and Biligrafin® 30% after injection of Urografin® 60% in a diagnostically recommended dose of 0.5 ml/kg, the maximum concentrations of free plasma histamine were found to be significantly elevated to the same range as after application of the already



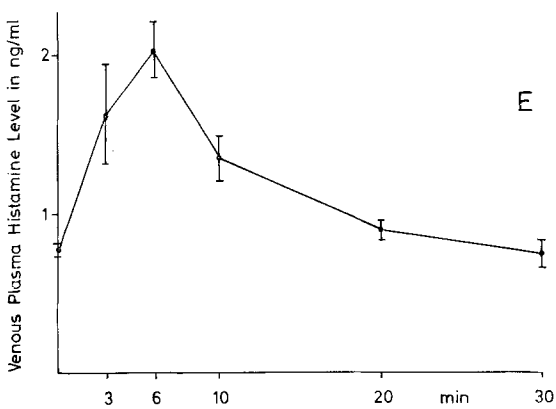
B 0.4 ml/kg iodipamide (Biligrafin® 30%) (n = 5),



D 0.5 ml/kg diatrizoate in form of Urovison® 58% (n = 6),



C 0.5 ml/kg diatrizoate in form of Urografin® 60% (n = 6),



E 0.75 ml/kg diatrizoate in form of Urovist® 65% (n = 6),

mentioned contrast media: 1.97 ± 0.21 ng/ml ($n = 6$, $p < 0.0005$). But the values declined to normal faster than after injection of Joduron® 70% or Biligrafin® 30%. 10 minutes after injection of Urografin® 60% the average level of free histamine was already significantly lower than 6 minutes after the injection ($p < 0.05$) (Fig. 1 C).

Only 2 out of 6 volunteers complained about heat feeling or feeling of epigastric pressure respectively.

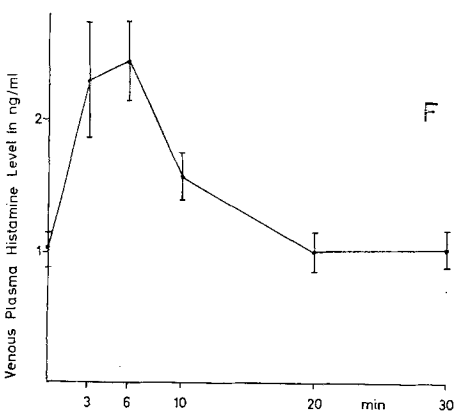
(5) Liberation of histamine by Urovison®

Urovison® 58% in a dose of 0.5 ml/kg, i.e. 0.29 g contrast medium/kg, liberated histamine in the same manner as Urografin® 60% (Fig. 1 D). Also the decrease of free histamine in plasma after reaching the maximum values corresponds well to the Urografin study. The difference between the mean values 6 and 10 minutes after injection was also statistically significant ($p < 0.05$). 3 out of 6 persons complained about nausea.

In 3 persons Urovison® 30% given in a dose of 4 ml/kg by 7 minutes infusion, i.e. 0.17 g contrast medium/kg × minute, failed to result in a perceptible liberation of histamine. None of the volunteers complained about any side effects.

(6) Liberation of histamine by Urovist® 65%

Urovist® 65% (0.75 ml/kg) effected an increase of free histamine in plasma in the same way as Urografin® 60% and Urovison® 58% did (Fig. 1 E). After 6 minutes the maximum concentration increased from 0.77 ± 0.03 ng/ml to 2.02 ± 0.17 ng/ml, and then decreased significantly already 4 minutes later to 1.35 ± 0.14 ng/ml ($p < 0.05$). 5 out of 6 volunteers complained about heat feeling (4) or nausea (1).



F 0.5 ml/kg iothalamate (Conray® 70%) ($n = 6$).

(7) Liberation of histamine by Conray® 70%

Figure 1 F shows the results obtained by injection of Conray® 70% in a dose of 0.5 ml/kg. After 3 minutes the histamine concentration rose rapidly ($p < 0.01$), just as it decreased thereafter ($p < 0.025$). Only 2 out of 6 persons reported to have had a feeling of warmth for a short time or of nausea respectively.

(8) Histamine levels after the injection of dextrose 50%

3 persons, receiving 0.5 ml/kg dextrose-solution 50% i.v., did not show any increase of free plasma histamine until 30 minutes after injection. None of these volunteers complained about side effects.

Discussion

In the course of application of different drugs liberation of histamine is widely accepted as reason for unpleasant side effects [47, 53, 54]. Nevertheless, with modern reliable methods an increase in free plasma histamine – especially during severe complications – has only been shown for a few of these drugs [5, 35, 36, 38]. Although liberation of histamine by contrast media has been discussed frequently [24, 32, 40, 83], the results of BRASCH et al. [2] and ROCKOFF and AKER [66] seemed to contradict a regular histamine liberation following the injection of contrast media.

But neither BRASCH et al. [2] nor ROCKOFF and AKER [66] studied histamine liberation in connection with standardized application of drugs. So their results are not strictly comparable with the experiments presented here.

Our results show that usual doses of chemically different contrast media lead to comparatively stereotyped increase and afterwards decrease of plasma histamine levels in venous blood of healthy persons. Within about 6 minutes after injection of a single agent the plasma histamine rose from less than 1 ng/ml plasma to about 2.0–2.5 ng/ml. 20 minutes after the injection the elevated concentrations had returned to almost normal levels. When estimating histamine in venous blood its liberation by contrast media from tissues or blood cells [61] into the plasma may partly be masked by the elimination of free histamine during blood passage through different tissues [80].

Many authors emphasized to inject the necessary dose of contrast medium very quickly. In this way unpleasant side effects are supposed

to be rarer than after slow injection of the same dose [6, 13, 15, 42, 60, 87–89]. This is even true for the old pyridones, which are no longer in clinical use because of their toxic side effects [1]. It should to be pointed out that Joduron® 70% did not elevate the plasma histamine levels more than less toxic contrast media. This does not mean that pyridones are as compatible as derivates of triiodobenzene because other factors than liberation of vasoactive amines certainly contribute to the compatibility of contrast media [17, 24, 32, 40, 50, 74, 83]. However the slower decrease of elevated histamine levels after pyridone injection in comparison to modern contrast media for urographic studies may indicate a possible factor in toxicity.

Biligrafin® was not the first contrast medium for i.v. cholecystography [23, 62, 81] and obviously today better compatible agents are available. In the presented studies Biligrafin was taken as a substance which is still in clinical use and causes severe side effects [10]. By no way it is an optimal contrast medium for i.v. cholecystography today [9, 12, 14, 20–22, 28, 69, 78, 85]. It seems quite evident that only the oral, though less risky cholecyst-cholangiography [16, 68] does not suffice to solve all X-ray problems concerning the gallbladder. So in many patients an i.v. contrast medium or even an infusion has to be employed [3, 7, 9, 55, 82, 86].

The three preparations of diatrizoates – Urografin® 60%, Urovison® pro injectione 30% Urovison® 58% respectively and Urovist® 65% – differ only in salt composition: Urografin® is mainly prepared as Na-salt, Urovison® mainly as methylglucamine and Urovist® totally as methylglucamine. All diatrizoate preparations were tested for histamine liberating capacity because there are differences in toxicity between Na-salts and methylglucamines [11, 26].

The viscosity of equimolar solutions of contrast media decreases with growing Na-content and increases with growing methylglucamine content [84]. Already ZINNER and GOTTLOB [88] and SWART and DINGENDORF [75] discussed possible differences in biological compatibility of contrast media solution basing on different viscosity. In comparable doses/minute there were no differences in histamine liberating capacity of the different diatrizoate salts. But reduction of the contrast medium dose/minute to 0.17 g/kg stops histamine liberating capacity. So finally higher doses of diatrizoates may be ineffective in liberating histamine when infused over some minutes. Urography, infusing contrast media – a method recommended manifold [27, 67, 72, 76, 77, 79] – possibly may be less dangerous for the patient especially concerning side effects coming from overshooting histamine concentration. Correspondingly FRANK and ZINNER [8], MEYER-BURG [44], and WILHELM and RICHTER [86] found a better tolerance of high doses of Biligrafin® and HERMS et al. [18] of a special Bilivistan®-preparation, when given by infusion instead of rapidly being injected. Also propanidid leads to a more pronounced histamine liberation when injected by shoot instead of slow injection [37].

Iothalamate in the form of Conray® 70% (0.5 ml/kg), if injected i.v. within 1 minute, liberates histamine as Urografin® 60% does. Hereupon it should be pointed out that Conray® did not interfere with the fluorometric measurement of histamine in plasma [2]. Also using Urovison® 30% interference of the contrast medium with histamine estimation did not come out. Therefore the fluorescence in the analytical samples can be related really to histamine.

The effects of contrast media on histamine release are specific because dextrose solution rapidly injected in order to mimic the osmotic effects of the contrast media, did not show any effects upon histamine levels in plasma. The values of osmotic pressures of various solutions injected are summarized in the table. Accordingly histamine liberation is not a simple consequence of an elevated osmotic pressure in blood, which already exclusively may lead to vasodilatation [19].

Osmotic pressure (at) of various contrast media and 50% dextrose solution.

	Osmotic pressure (at)	
Biligrafin® 30%	9.4	(37 °C)
Conray® 70%	49.6	(38 °C)
Joduron® 70%	66.0	(37 °C)
Urografin® 60%	38.0	(37 °C)
Urovison® 58%	42.0	(37 °C)
Urovist® 65%	39.0	(37 °C)
T 50% = Dextrose 50%	70.4	(37 °C)

Average levels of free histamine in venous plasma of volunteers after i.v. injection of

The apparent contradiction of the presented results to those of BRASCH et al. [2] and ROCKOFF and AKER [66] may be explained by different speeds of contrast media injection. This corresponds to the lack of histamine release during infusion of Urovison® 30%.

There was no relation to be observed between liberation of histamine on one hand and occurrence of side effects of the other hand. But the results did not suprise in face of the different mechanisms of uncommon actions of contrast media. In some cases with unaphylactoid reactions against contrast media overwhelming liberation of histamine may be a potent factor in the development of unpleasant complications according to the results with propanidid [38].

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