HAZARDS OF INTRA-ARTERIAL INJECTION OF HYDROXYZINE*

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ACCIDENTAL intra-arterial injection of some drugs may cause extensive tissue necrosis. Most of the early reports of sequelae of intra-arterial injections resulted from the use of 5 or 10 per cent thiopentone (Pentothal®).¹⁻³ More recent reports record the occurrence of severe necrosis and gangrene following meperidine (Demerol®) and promethazine (Phenergan®), promazine (Sparine®), amobarbital,⁴ bromsulfaphthalein, amphetamine,⁵ pentobarbital,⁶ and chlorpromazine.⁷ Not only may such accidental intra-arterial injections result in severe complications, but the usual treatment with vasodilating drugs, sympathetic block, and heparinization has been notably ineffective.^{3,4,6,8-10}

Our attention was called to the hazards of yet another drug by the tragic sequence of gangrene and amputation of the forearm of a young woman following a 2 ml injection of hydroxyzine (Vistaril®) intended as an intravenous sedative during regional anaesthesia for an operation on the other arm. This presumably intra-arterial injection was made with a 23-gauge needle directly into a vessel in the antecubital space. There was immediate complaint of pain and recognition of the incipient problem. Treatment included flushing of the artery with local anaesthetic, papaverine, and sympathetic block. Gross examination after amputation revealed that all major vessels were still patent.

Subsequently a study was begun comparing hydroxyzine with some other potentially hazardous drugs using New Zealand white rabbits. Intra-arterial injections were made in or around the central artery of the ear.

RESULTS OF STUDY

In the dosage used, injection of meperidine 12.5 mg (0.25 ml) or propiomazine (Largon®) or saline produced no remarkable changes. However, the injection of hydroxyzine 12.5 mg (0.25 ml) either intra-arterially or peri-arterially was invariably followed by extensive tissue damage. The immediate effect of intra-arterial injection of hydroxyzine was blanching of the entire ear followed by a deepening cyanosis. Twenty-four hours later the ear was so oedematous that it could not be held in its upright position. Cyanosis persisted along with the oedema, and in twelve to fifteen days the process progressed to dry gangrene involving the full thickness of the ear in an elliptically shaped area usually 1 to 1.5 cm in the longest dimension. The final result was a hole in the injected ear.

Peri-arterial injections were sometimes unavoidable. Although these were far from innocuous, full thickness necrosis never resulted. The typical course was an immediate blanching of 1 to 2 cm in diameter in the area of injection, followed

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by oedema. Healing was characterized by crust formation over the point of injection, and gradual improvement over a thirty-day period.

Dilution of hydroxyzine to 25 mg/ml (1:2) did not noticeably alter the gross or microscopic changes in the ears subsequent to intra-arterial or peri-arterial injection.

Histologic studies were made at selected intervals after injections of hydroxyzine and before the gangrene was grossly apparent. Following intra-arterial injection of 0.25 ml (12.5 mg) of hydroxyzine, individual rabbits were sacrificed at two, three, and eight days. Several sections of each ear were prepared for microscopic examination. The following changes were observed:

At 48 hours, extreme oedema, acute inflammation with diffuse cellular infiltration, involvement of the injected side of the ear only, and no necrosis, thrombosis, or vasculitis.

At 72 hours, moderate oedema, localization of acute inflammation, acute arteriolitis and venulitis, poorly organized thrombus, and inflammation on both sides of the cartilage of the ear.

After 8 days, extensive oedema, acute inflammation, necrosis of the connective tissue, thrombi with early organization, and both sides of cartilage involved.

The immediate blanching was interpreted as severe ischaemic vasoconstriction. The subsequent cyanosis probably reflects venous stasis as a result of the oedema, and from which thrombosis was also a consequence. This is consistent with the pathologic sequence after intra-arterial injection of thiopentone as described by Stone and Donnelly in their excellent review article.¹⁰ It should be noted also that in order to produce gangrene routinely after injection into the femoral artery of dogs it was necessary to stop blood flow by proximal occlusion prior to injection,⁵ and thus to prolong the time of contact between concentrated drug and arterial walls.

ATTEMPTED TREATMENT

An attempt was made to prevent progress to gangrene after intra-arterial hydroxyzine by injecting either lidocaine, tolazoline (Priscoline®), papaverine, phentolamine (Regitine®), or dexamethasone (Decadron®) into the artery immediately after the hydroxyzine. Both lidocaine and papaverine did prevent the otherwise inexorable progress to full thickness necrosis. The oedema and cyanosis were apparent during the first week, but then lessened and disappeared with recovery in two weeks. Tolazoline and phentolamine gave variable results and were not pursued. The results using dexamethasone intra-arterially were more dramatic. If the intra-arterial hydroxyzine was followed immediately by intra-arterial dexamethasone 0.4 mg (0.1 ml), oedema did develop, but cyanosis was never marked, and the ear appeared normal in one week.

In three rabbits both peri-arterial and intra-arterial injections were made with 0.25 ml (12.5 mg) hydroxyzine. In each instance one ear would receive the peri-arterial, and the other ear the intra-arterial injection. Each rabbit was then immediately given dexamethasone 1 mg intramuscularly, and 1 mg twice a day for one week. The ears receiving the peri-arterial injections developed only local oedema and blanching, which disappeared after five days of treatment.

Two rabbits given intra-arterial hydroxyzine completely recovered following intramuscular dexamethasone, 1 mg twice a day for one week. One healed in three weeks, the other in seven weeks. However, one rabbit thus treated went on to full thickness necrosis of an area of the ear similar to that previously observed in untreated rabbits.

The benefit of immediate *intra-arterial* dexamethasone into the affected arterial tree appears to be much greater than systemic effects, as demonstrated in an additional rabbit in which one ear was injected intra-arterially with 12.5 mg hydroxyzine followed by intra-arterial dexamethasone 0.4 mg while the opposite ear received only the intra-arterial hydroxyzine. The treated ear developed slight oedema, minimal cyanosis, and no necrosis, while the other ear developed the usual sequence of pathologic change ending in necrosis of part of the ear. Results were similar in another rabbit that had intra-arterial hydroxyzine followed by dexamethasone through the same needle, and a peri-arterial injection in the other ear. The intra-arterial injection was almost harmless, while the peri-arterial injection caused the typical development of blanching, oedema, crust formation and slow healing.

DISCUSSION

Iatrogenic necrosis and gangrene of an extremity in an otherwise healthy patient is a consequence we would all most devoutly wish to avoid. Prevention of such a catastrophic event is obviously more desirable and more effective than any treatment afterwards.

Hydroxyzine is clearly a clinically hazardous drug if injected intra-arterially. Instances of permanent damage cast doubt on whether the temporary benefits of using such a drug ever can be worth the hazard. Certainly every precaution should be taken to avoid inadvertent intra-arterial injection of hydroxyzine. These include: (*a*) avoidance of this drug where possible; or (*b*) introduction by means of an obviously well-functioning venoclysis; or (*c*) if direct intravenous injection is attempted this should be done with a needle large enough to provide obvious pulsatile reflux of blood in the event that an artery is accidentally entered; and (*d*) areas such as the antecubital fossae, back of the hand, and the wrists, which are known for the occurrence of aberrant superficial arteries,¹¹⁻¹³ should be avoided for direct injection.

Hydroxyzine either intra-arterially or peri-arterially can produce marked inflammatory and oedematous changes of the rabbit ear which result in ultimate necrosis. Thrombosis does not appear to be an early consequence of this irritant. The striking feature is an acute inflammatory process, probably the result of cellular necrosis in the arterial wall itself, and around the arterial distribution.^{3,10} Serious sequelae were prevented by immediately flushing the artery with lidocaine or papaverine, probably on the basis of rapid reversal of the intense vasoconstriction and thus reduction of the time of contact with the concentrated irritant.⁵ The use of dexamethasone (Decadron®) intra-arterially prevented the extreme necrosis otherwise commonly observed. These results in the rabbit seem to warrant clinical use of intra-arterial corticoids immediately after accidental intra-arterial injection of noxious medications.

The fact that even peri-arterial injections of hydroxyzine produced damage in the rabbit ear is worrisome in view of the common clinical practice of requesting nurses to inject this drug intramuscularly for sedation in obstetrics. The validity of this latter concern is suggested by an instance of gangrene of the forearm after intramuscular injection of chlorpromazine into the anterior aspect of the biceps.¹⁴

SUMMARY

A case of gangrene and amputation of the forearm following presumed intra-arterial antecubital injection of hydroxyzine is reported.

Studies were made of rabbits given intra-arterial and/or peri-arterial injections of meperidine, propriomazine, hydroxyzine, or normal saline. Only following the injection of hydroxyzine did severe pathological changes regularly occur. These changes were mitigated by the immediated intra-arterial injection of dexamethasone (Decadron®). Flushing the artery with papaverine or lidocaine, although beneficial, seemed to offer less protection.

RÉSUMÉ

Nous racontons l'histoire d'un cas de gangrène et d'amputation d'un avant-bras à la suite d'une injection d'hydroxyzine présumée intra-artérielle antécubitale. Chez des lapins, nous avons fait des études à la suite d'injections intra-artérielles et/ou péri-artérielles de mépéridine, de propriomazine, d'hydroxyzine ou de sérum salé normal. Des modifications pathologiques graves ne sont apparues qu'à la suite des injections d'hydroxyzine. Ces modifications furent limitées par l'injection immédiate intra-artérielle de décaméthodone. Le lavage de l'artère avec de la papaverine ou de la lidocaïne, bien que bénéfique, nous a paru offrir moins de protection.

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