Relevance of Plasma Histamine Levels to Hypotension

To the Editor:—A number of recent articles have appeared in *Anesthesiology* implicating histamine release as a significant mechanism for hypotension produced by drugs (particularly morphine).

High concentrations of morphine clearly can produce histamine release in nonallergic subjects as evidenced by a wheal and flare response after intradermal injection, by leukocyte histamine release, and by elevations in plasma histamine levels in some patients receiving high doses of morphine during surgery. On the other hand, we seriously question the inference that histamine release *per se* is responsible for a major portion of the cardiovascular effects of morphine.

The histamine released by morphine presumably originates from mast cell and basophil granules, which contain other vasoactive substances. Furthermore, mast cell and basophil degranulation may be accompanied by release of rapidly synthesized mediators, such as eicosanoids and bradykinin. These other mediators, whose plasma levels do not necessarily parallel those of histamine, may be responsible for more of the cardiovascular effects associated with mast cell degranulation than the histamine itself. Morphine, in addition, has multiple direct effects on the vasculature.

In a recent editorial in *Anesthesiology*, it was stated that "increases of 2 to 5 ng/ml are invariably associated with tachycardia, widespread flushing and urticaria and increases above 5 ng/ml with severe hypotension." We are unable to determine the patient population underlying this statement, since all three references seem to refer to the same one patient. This patient had cold urticaria and became hypotensive following immersion of a hand in cold water. Histamine levels in the cooled arm were 240 ng/ml compared with 5 ng/ml in the other arm. The histamine levels in mixed venous blood must have been somewhere between these two values. A recent study by Atkins et al. measuring histamine levels during antigen aerosol challenge showed peak histamine levels ranging from 18 to 60 ng/ml in five of six subjects without significant hemodynamic abnormalities. The sixth patient who became hypotensive had a peak plasma level of 80 ng/ml. Similarly, during a study of immunotherapy for insect hypersensitivity reported by Smith et al., insect venom increased plasma histamine into the 2 to 10 ng/ml range without eliciting hypotension, and sometimes without even producing urticaria. Three patients with plasma histamine levels above 10 ng/ml (two above 50 ng/ml) were severely hypotensive, but did not manifest urticaria.

Fahmy recently reported a severe hypotensive episode following iv administration of morphine and associated with a histamine level of 20 ng/ml. However, another case report from the same institution showed histamine levels of 40 ng/ml following anaphylactoid reaction to succinylcholine, which did not involve significant hypotension.

To summarize, the relationship between magnitude of histamine release and magnitude of cardiovascular effects appears unpredictable. Furthermore, although changes in histamine level following morphine have shown some correlation (r = 0.81) with decreases in systemic vascular resistance, this in no way implies causation.

If histamine is important in producing hypotension, one ought to be able to block the hypotension by histamine receptor antagonists. A recent paper from the same institution attempted this and claimed success. However, their data shows an increase in heart rate and blood pressure in patients receiving diphenhydramine, and even more so in those receiving the diphenhydramine-cimetidine combination. One wonders if a dose of atropine, producing comparable increases in heart rate, might not have produced the same protective effect as the diphenhydramine-cimetidine combination.

While we are in no way challenging the relative hypotensive effects of morphine, as opposed to other narcotic analgesics, we do not feel that the evidence presented so far indicates that morphine-induced hypotension is necessarily related to the release of histamine into the systemic circulation.

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References

In reply.—We have read with interest the letter by Hirshman et al., and are frankly somewhat puzzled by the point they are attempting to make.

We are criticized specifically for suggesting a relationship between histamine release and cardiovascular effects. To bolster their argument they inappropriately refer to data we published concerning an anaphylactoid reaction following succinylcholine which did not involve significant hypotension.1 If they would care to re-read the article, they will note that 1,500 ml of lactated Ringer’s solution was infused rapidly to avoid hypotension. Nonetheless, there was a rapid and profound decrease in SVR.

The relationship between histamine release, not involving anaphylaxis, and decrease in SVR is certainly significant, as we and others have reported.2-5 We agree that our correlation2 taken as an isolated report does not necessarily imply causation. However, when the effect on SVR can be prevented by histamine antagonists as we reported,6 it seems reasonable and prudent to conclude a causal relationship exists. We agree that this technique is far from perfect, but it is the classic and universally accepted method of determining causality.

The histamine antagonists had no significant effect on SVR. Furthermore, when heart rate is not affected, comparable results are obtained.7 We have also obtained the same results when chlorpheniramine is substituted for diphenhydramine and there is no increase in heart rate. The suggestion about atropine borders on the ridiculous.

It appears that Hirshman et al. accept that morphine can decrease SVR, that morphine can cause histamine release, and that histamine can cause a decrease in SVR. We have demonstrated that histamine antagonists prevent much of the decrease in SVR associated with morphine as well as other histamine-releasing drugs.

We appear to have a webbed and billed bird that quacks. It might be a Canterbury in disguise, but it seems more realistic to call it a duck.

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REFERENCES

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