"Unresponsiveness" to Isoproterenol

The report by Trautlein et al (see page 711) presents the startling finding of apparent unresponsiveness to administration of isoproterenol (they use the term "paradoxical bronchospasm") in patients whose airways respond to inhalation of both isoetharine and of terbutaline. We do not wish to go on record as denying this possibility, but the observation provides a nice opportunity to discuss the variables and pitfalls that must be dealt with before accepting this pharmacologic inference.

Briefly, these patients had been previously shown to have "reversible airway disease" (a reversible component?) on a previous testing occasion using inhalation of isoetharine. Their nonresponsiveness to administration of isoproterenol sulfate (250μg by cartridge nebulizer) was verified on a repeat occasion, both trials occurring when the patients' disease was stable and they were asymptomatic. Subsequently, they responded to inhalations of terbutaline on several occasions.

For such an important question as this, it is mandatory that the reader be provided with the individual data on the conditions and response for each challenge, as well as the individual characterization of the kind of disease being studied, so that a thoughtful appraisal can be made at the time of publication and in retrospect. Trautlein et al provide little of these data, and their discussion is virtually nonexistent. Details such as the form, dose, and mode of delivery of isoetharine (Bronkosol solution by intermittent positive-pressure breathing or a Bronchaid cartridge nebulizer?), the dose of terbutaline sulfate, the individual diagnoses of the patient (asthma? chronic bronchitis? underlying emphysema?), and the details of the response on their other trials are not provided, and the report to which Trautlein et al refer gives no individual data. Measurements of airway resistance are not made. We have no information on the therapy received prior to each trial, except that the patients were receiving therapy with bronchodilator drugs which did not include isoproterenol.

Why should this information be important? Among the phenomena circulating in the literature on bronchodilator drugs, the following may be relevant:

First, the maximum expiratory flow-volume (MEFV) maneuver is complex. The flow achieved is currently described according to the equal pressure point (EPP) theory, which states that the airway is divided into an upstream and downstream segment from the EPP, at which point the pressure within the airway equals the pressure without. Flow is directly proportional to the elastic recoil of the lung and inversely proportional to the resistance of the upstream segment. This resistance of the upstream segment is inversely proportional to the square of the cross-sectional area at the EPP and directly proportional to the length of the upstream segment.

An added variable is the compliance of the airways. When the inherent rigidity of the airway is enhanced, expiratory pressure is less apt to constrict it. Thus, contraction of smooth muscle induced by acetylcholine is actually associated with an increase in flow through the isolated canine trachea at high driving pressures because of less tendency to collapse, whereas administration of isoproterenol, by diminishing tone, increases the normal airway compliance and renders the airways more compressible.

With their collapse, the EPP moves toward the carina, increasing the length of the upstream segment, decreasing the cross-sectional area, and, therefore, increasing resistance. Although the effect of a bronchodilator drug is usually to increase flow, particularly where excessive tone exists, it is possible to speculate that the net effect may sometimes be no change or a reduction in flow because of the effect on one or more of these variables.

By administration of isoproterenol to normal subjects, McFadden et al demonstrated a reduction of elastic recoil accompanied by only small changes in flow, despite considerable decreases in airway resistance. This effect was dose related, occurring with a 1-percent solution of isoproterenol but inconsistent at a concentration of 0.5 percent or less. McFadden et al contended that the reduction in elastic recoil tends to negate the increase in airway resistance.
diameter, with little net improvement of forced flows. Yet another variable is the observation that maximum inhalation preceding MEFV maneuvers is associated with bronchodilatation. This might obscure the effect of a bronchodilator drug.

The characteristics of the pulmonary disease being treated are extremely important. Using smaller doses of isoproterenol than McFadden et al and a variety of patients with chronic obstructive pulmonary disease, Boushy detected no systematic effects of isoproterenol on elastic recoil, but nevertheless observed significantly less improvement of forced flows in those patients with preexisting severe loss of elastic recoil due to emphysema. On the other hand, patients with morphologic evidence of chronic bronchitis (Reid index) in resected specimens responded significantly better to administration of isoproterenol than those without this finding. Boushy attributed the lack of a bronchodilator-induced response of the expiratory flow in this population with chronic obstructive pulmonary disease to an increased collapsibility of the large airways, rather than to a lack of response to administration of isoproterenol, since in all patients measurements of airway resistance showed comparable improvement. McFadden et al points out that although asthmatic patients usually decrease their static compliance when given bronchodilator therapy, increased compliance has been observed. In the study of Trautlein et al, variables in dosage may be involved, and certainly we should know the characteristics of the patients being compared.

Secondly, it is well known that the propellant aerosol per se can induce bronchoconstriction. A recent short note by Bryant and Pepys succinctly points this out. They found three asthmatic patients who experienced wheezing with the beclomethasone inhaler. The propellant vehicle itself caused marked reductions of the forced expiratory volume in one second (FEV₁) that were most pronounced at five minutes and required 45 to 60 minutes to clear. Addition of salbutamol to the inhaler more than offset the effect. It is easy to visualize certain asthmatic or chronic bronchitic patients with sensitive bronchial irritant receptors who fail to respond adequately to certain marketed preparations because the stimulation of these receptors overrides the effect of the bronchodilator drug at that dosage.

Thirdly, it is clinically recognized that responses to bronchodilator drugs are not consistent, even to the same agent. If one begins with a lack of response as the index trial, the other trials will appear to be significantly better simply through the selection process. Trautlein et al are somewhat protected from this pitfall, and must be commended for it, by their insistence on two trials with isoproterenol and selection of the greater response; however, patient 2 in their series in Table 2 was no longer a non-responder by their criteria. Moreover, the high initial values for patients 6 and 10, if already well into the predicted normal range, would have allowed little room for improvement and might have precluded any significant response on that basis. Freedman has stressed that the responses in FEV₁ are dependent on the initial value, as noted by Hume and Gandevia. When absolute responses in FEV₁ on different occasions in the same patient are plotted as a function of initial FEV₁, the curve is bell shaped, with responses maximum in a middle range but falling off sharply, sometimes to negligible values, as the asthma either becomes severe or enters remission. Furthermore, some patients respond unpredictably from the same FEV₁. Patient 12, with an initial FEV₁ of 700 ml and a drop 120 minutes later to 400 ml, may have been on the unresponsive end of this curve. We have found this type of response in patients with severe asthma who are forced to refrain from using their inhaler for 120 minutes after its use, but have severe disease, are asymptomatic, and use their inhaler excessively. This is presumably "rebound bronchoconstriction" secondary to receptor tolerance. Patient 9 similarly has quite severe asthma and might be in the relatively unresponsive range of Hume and Gandevia at the time of this test.

Fourthly, the pharmacologically important question is whether nonresponsiveness of the bronchial β₂-adrenergic receptors can occur with one agonist, but not to another of differing specificities. Although the patients had not used isoproterenol for a year or more, could they be relatively unresponsive to isoproterenol because of partial tolerance produced from their β₂-adrenergic therapeutic agents? Conolly et al have provided an interesting analogy, showing that either small continuous doses of isoproterenol or a single dose of a long-acting β₂-adrenergic agent will cause subsensitivity of the response of the heart rate to challenge with isoproterenol in dogs, whereas a large single dose of isoproterenol does not. Guinea pigs were subsequently less able to tolerate bronchoconstriction due to histamine. This subsensitivity was also produced in man. In vivo data in man during treatment with oral sympathomimetic agents are becoming available which describe a significant reduction of multiple measurements of β₂-adrenergic response. Our own unpublished work has found that isolated quantitation of airway responses will reveal some impairment here also. Work recently presented showed that tachyphylaxis to isopro-
terenol in rat trachea can be consistently produced in vitro.\textsuperscript{20} Cross-tolerance to and from other β-adrenergic agonists is under study and has been reported by others;\textsuperscript{15} however, the field is still controversial, with a number of conflicting reports. Nevertheless, the possibility of subsensitivity from previous sympathomimetic therapy, perhaps a highly variable factor from one individual to the next, must be considered in evaluating the data of Trautlein et al.

It has been shown that the weak α-adrenergic (pressor) effect of isoproterenol on the vasculature can be uncovered by producing tachyphylaxis to isoproterenol by prolonged in vitro exposure.\textsuperscript{21} Simonsson et al.\textsuperscript{22} have demonstrated, both in vivo and in vitro, the existence of α-adrenergic receptors in human airways by using suitable blockers and an α-adrenergic agonist. A fascinating in vitro potentiation of α-adrenergic contraction by endotoxin was shown, much magnified in a patient with chronic bronchitis. Could the tolerance of the β-adrenergic receptors in man, particularly in patients with chronic bronchitis, uncover a similar response to isoproterenol?

The possible mechanisms of direct irritation from two inhalations of isoproterenol itself or the formation of the 3-methoxy metabolite of isoproterenol causing β-adrenergic block seem remote to us and to Trautlein et al. In fact, the latter mechanism has been discounted by its original proponents, particularly because agents not producing the metabolite still produce β-adrenergic tolerance.\textsuperscript{16}

The data of Trautlein et al are provocative and still very useful. They document a perplexing phenomenon. Carping at the lack of further information does not quite get us off the hook. Their report is suggestive, at least, that the majority of these nonresponders are probably not inhaler “abusers” but fail to respond for other reasons yet to be determined, perhaps for some of the reasons mentioned herein.

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REFERENCES


