Rhabdomyolysis and Beta Adrenoceptor Agonists

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Dear Sir,

We read with interest the case report 'Rhabdomyolysis and acute renal failure after terbutaline overdose' by Blake and Ryan [1] in your September issue. In this context it may be of interest to note that two other cases of β_2 -adrenoceptor agonist-induced rhabdomyolysis have been described [2, 3]: one case after therapeutic oral doses of fenoterol for tocolysis [2], and the other case after an overdose of terbutaline [3]. These cases confirm the observation made by Blake and Ryan.

As pointed out by the authors cases of rhabdomyolysis following amphetamine have also been described [4]. In addition, other adrenergic agents such as methamphetamine, phenmetrazine, methylenedioxymphetamine, phenylpropanolamine, D-norpseudoephedrine, and fenfluramine [4-8] have been implicated in the pathogenesis of rhabdomyolysis. There is, therefore, considerable evidence that under certain conditions adrenergic substances may have a myotoxic potential and cause rhabdomyolysis.

As to the mechanism underlying the myotoxicity of β_2 -adrenoceptor agonists, however, we do not think it probable that ischemia plays a major role: ischemia may partly explain the rhabdomyolysis of indirectly acting adrenergic agents like amphetamine, since these substances predominantly release noradrenaline and thus may favor α -adrenergically mediated vasospasm. β_2 -Adrenoceptor agonists like fenoterol and terbutaline, however, have predominantly vasodilator effects. Thus, we think it more likely that their myotoxic effects are, in fact, metabolic and are related to depletion of muscle energy stores induced by glycogenolysis and lipolysis, rather than by ischemia. These effects may be aggravated by tremor and agitation which are both common side

effects of β_2 -adrenoceptor agonists. In contrast, both mechanisms – metabolic stress and ischemia – may work in intoxications through amphetamine-like substances: this may partly explain, why reports on myotoxic effects of amphetamine are rather common, whereas such reports are rare for β_2 -adrenoceptor agonists.

Last but not least, we would like to comment on the statement of the authors that 'serum and urine myoglobin measurements are an unreliable means of detecting rhabdomyolysis': this statement – although commonly repeated in the literature – is not valid [9]. The opinion that in spite of major muscle necrosis myoglobin is not released in sufficient amounts into plasma and excreted into urine dates from an era in which reliable and sensitive assay systems for myoglobin measurement did not exist and when myoglobin was measured by spectroscopic or gel immunodiffusion methods. Indeed, it is difficult to conceive that a relatively low molecular

weight molecule like myoglobin would not be released on major muscle damage, whereas high molecular weight enzymes like creatine kinase would be released. This assumption is also contradicted by myocardial infarction where myoglobin release has been shown to be more sensitive than creatine kinase [10]. When using sensitive RIA methods [10] myoglobin is consistently elevated during rhabdomyolysis [9]: this is especially true for serum determinations, if renal failure supervenes and myoglobin is retained because of a diminished renal clearance. We have now experience with 138 cases of rhabdomyolysis: it was possible to diagnose myolysis by myoglobin RIA in serum or in urine in all cases. Myoglobin often remains elevated for a longer period than creatine kinase, if renal failure is present, thereby allowing diagnosis at a time, when creatine kinase has already reached normal or near normal values.

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