

## Antivenom efficacy, safety and availability: measuring smoke

*Improving safety is important, but in many regions antivenoms are not available*

ALTHOUGH SNAKEBITE HAS BEEN a subject of medical interest since antiquity, and despite it continuing to affect millions of people annually,<sup>1,2</sup> it remains one of the neglected health problems of the tropics.<sup>1-3</sup> Today, almost lost amidst the preoccupation with shortages of vaccines and antiretroviral medication in the developing world, there is a crisis in antivenom availability in the very same nations.<sup>3</sup> In response, the World Health Organization recently held its first antivenom workshop in more than 20 years, to discuss the global supply and quality of antivenoms.<sup>4</sup> However, perhaps more importantly, a growing community of physicians from the regions with the greatest snakebite burden have become more active in seeking solutions to at least some part of this ancient problem.

The study by Gawarammana and colleagues in Sri Lanka (*page 20*) is one example of such scholarship.<sup>5</sup> It is a welcome addition to the relatively scant clinical trial literature examining the management of snakebite. In a well conducted but underpowered study, the authors document a reduction in mild-to-moderate acute reactions to antivenom with an antihistamine bolus in conjunction with a hydrocortisone infusion. However, in the clinically important endpoints of moderate and severe reactions, there was insufficient power to confirm a trend toward fewer reactions in the hydrocortisone-containing regimens. This study is in contrast to a previous study from Brazil that failed to

demonstrate any difference in early antivenom reactions with prophylactic promethazine alone.<sup>6</sup>

Most notable in this and an earlier Sri Lankan study,<sup>7</sup> which assessed subcutaneous adrenaline as prophylaxis against acute antivenom reactions, was the extremely high rate of such reactions — in this study, almost half the patients had moderate or severe reactions sufficient to require adrenaline. This differs considerably from the rates in Australia (reported as 10% in the absence of premedication<sup>8</sup> and 4.6% with premedication<sup>9</sup>). Snake antivenom is derived from antibodies of immunised animals; the rates of reactions appear to vary with the species of antibody origin, the extent of pepsin digestion, the presence of molecular aggregates and the total protein content of the product.<sup>4,10</sup> It has been presumed that most acute reactions relate to the extent of complement activation from Fc receptor binding,<sup>10,11</sup> with improvements in quality having largely resulted from enhancements in antivenom processing.<sup>4</sup> However, the recent WHO workshop called for a re-examination of old assumptions concerning such reactions and, consequently, what constitutes “best practice” for antivenom manufacture and administration.<sup>4</sup>

Although Sutherland attributed the low reaction rate to Australian snake antivenoms to a series of refinements in the recommendations from the former Commonwealth Serum Laboratories concerning antivenom administration, includ-

ing the practice of prophylactic use of adrenaline and hydrocortisone,<sup>9</sup> current national reaction rates and associated clinical practice remain unclear.<sup>12</sup> It is intended that recently introduced refinements to the Australian coding standards for ICD-10-AM (third edition)<sup>13</sup> will assist in closing this gap in the national toxinology evidence base. However, because of the inherent delays in the collation of national statistics, and as current methods are far from complete,<sup>12</sup> it would seem appropriate to mandate reporting of adverse antivenom reactions to facilitate appropriate follow-up. Such a system is in place in Brazil.<sup>14</sup>

Meanwhile, there is a dichotomy in current premedication recommendations for reducing acute reactions to snake antivenoms in Australia. In Australia's toxinology textbook,<sup>15</sup> Sutherland and Tibballs considered the evidence available up to 2001 and concluded that "premedication with subcutaneous adrenaline is recommended (0.25 mg for an adult, 0.005 mg/kg for a child) before antivenom therapy". By contrast, a recent review by Currie concluded: "with the very low rate of severe reactions to antivenom seen in Australia... and the ability of emergency medicine physicians to adequately manage reactions that may occur, a policy of withholding premedication but always having adrenaline drawn up and ready is now recommended by many authorities and is policy in the Northern Territory".<sup>16</sup> In the middle is Australia's antivenom manufacturer, CSL Limited: "Some authorities have advocated premedication with subcutaneous adrenaline and intravenous antihistamine, particularly in those patients who are known to be at risk, but such use is controversial".<sup>17</sup> Readers should consult the references for further details of the respective arguments and the history and evolution of the manufacturer's recommendations.<sup>8,9</sup>

Although it is likely that well staffed major hospitals can, if it is recognised early, readily and rapidly manage antivenom reactions, such events can be severe, progressive and are not necessarily remediable.<sup>18</sup> Therefore, it is the small rural centres, with more limited staffing and facilities, that may benefit most from the apparent efficacy of adrenaline premedication.<sup>7,9,15</sup> If premedication is to be given, currently the best evidence is that it should be subcutaneous adrenaline.<sup>7</sup> However, it is notable that Sutherland himself was agreeable to some "alternative but equally effective replacement for adrenaline".<sup>9</sup> And so we return to the search in Sri Lanka for such a replacement (or adjunct).

The apparent benefit from the combination of an H<sub>1</sub> antagonist and hydrocortisone described here suggests that a combination of H<sub>1</sub> and H<sub>2</sub> blockers may bring additional benefit, as has been proven for the treatment of acute allergic syndromes.<sup>19</sup> However, the applicability of this study, in which a poor-quality antivenom resulted in extreme reaction rates, to the situation in Australia (where low reaction rates are reported) is uncertain. Interestingly, the antivenom used (the Haffine polyvalent snake antivenom) appears to be an equine Fab<sub>2</sub> product,<sup>20</sup> the same as that used in Australia.<sup>17</sup> The Indian antivenom that was used in Sri Lanka, however, is a lyophilised preparation<sup>5</sup>, whereas the Australian antivenom is a liquid product. Therefore, aside from the premedication issue,

there are clearly opportunities to improve the reaction rate by improved processing of this Indian product.<sup>4</sup>

Unfortunately, these debates are irrelevant for most people affected by snakebite, predominantly in the rural tropics. For example, in Papua New Guinea the high cost of Australian antivenoms puts adequate supplies beyond the reach of the health budget.<sup>2</sup> For people in countries where the available antivenoms are of poorer quality, studies such as these, even if they only demonstrate reductions in reaction rates from 80% to 50%, are applauded; more are sorely needed. But for most countries where antivenoms are unavailable or unaffordable, there is little to do but measure smoke from the burning house while praying for rain.

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