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Review article

Ricin as a weapon of mass terror — Separating fact from fiction

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ABSTRACT

In recent years there has been an increased concern regarding the potential use of chemical and biological weapons for mass urban terror. In particular, there are concerns that ricin could be employed as such an agent. This has been reinforced by recent high profile cases involving ricin, and its use during the cold war to assassinate a high profile communist dissident. Nevertheless, despite these events, does it deserve such a reputation? Ricin is clearly toxic, though its level of risk depends on the route of entry. By ingestion, the pathology of ricin is largely restricted to the gastrointestinal tract where it may cause mucosal injuries; with appropriate treatment, most patients will make a full recovery. As an agent of terror, it could be used to contaminate an urban water supply, with the intent of causing lethality in a large urban population. However, a substantial mass of pure ricin powder would be required. Such an exercise would be impossible to achieve covertly and would not guarantee success due to variables such as reticulation management, chlorination, mixing, bacterial degradation and ultra-violet light. By injection, ricin is lethal; however, while parenteral delivery is an ideal route for assassination, it is not realistic for an urban population. Dermal absorption of ricin has not been demonstrated. Ricin is also lethal by inhalation. Low doses can lead to progressive and diffuse pulmonary oedema with associated inflammation and necrosis of the alveolar pneumocytes. However, the risk of toxicity is dependent on the aerodynamic equivalent diameter (AED) of the ricin particles. The AED, which is an indicator of the aerodynamic behaviour of a particle, must be of sufficiently low micron size as to target the human alveoli and thereby cause major toxic effects. To target a large population would also necessitate a quantity of powder in excess of several metric tons. The technical and logistical skills required to formulate such a mass of powder to the required size is beyond the ability of terrorists who typically operate out of a kitchen in a small urban dwelling or in a small ill-equipped laboratory. Ricin as a toxin is deadly but as an agent of bioterror it is unsuitable and therefore does not deserve the press attention and subsequent public alarm that has been created.

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1. Introduction

In recent years, there has been heightened concern regarding the potential of various chemical and biological weapons as agents for urban terrorism (Gosden and Gardener, 2005). These concerns have been reinforced by the recent attempted uses of ricin by various groups in the United States and United Kingdom (Gibson et al., 2003; Mayor, 2003).

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Ricin is regarded as an ideal agent for terrorism (Franz and Jaax, 1997), partly because of its notoriety arising from the high profile assassination of a leading communist dissident in London during the late 1970s (Crompton and Gall, 1980). Furthermore, it is readily accessible, and its relative ease of extraction from the castor bean plant, as well as its stability in both hot and cold conditions (CDC, 2004), seem to make it a weapon of choice. It has been regarded as one of the most potent poisons in the plant kingdom (Lee and Wang, 2005) and has been described as a toxin that can cause death within minutes of exposure (Marshall, 1997). However, despite these assertions, does ricin ultimately warrant this reputation as an ideal weapon of mass terror?

2. Methods

We searched OVID MEDLINE (January 1950 to March 2009) and ISI Web of Science (http://www.isiknowledge.com) (1900 to March 2009) to identify all studies associated with the toxicity of ricin, the routes of exposure and mechanisms of toxicity; no restrictions were placed on year of publication. To identify the expected toxicity following exposure to ricin we used the terms ricin, *Ricinus communis*, toxalbumin, castor beans and ricinine which were combined with either poisoning, toxicology, pharmacology, routes of exposure, diagnosis, treatment or terrorism. Bibliographies of identified articles were screened for additional relevant studies including non-indexed reports. Non peer-reviewed sources were also included: books, relevant newspaper reports and applicable web material.

3. Mechanism of toxicity

Ricin is a toxic glycoprotein (toxalbumin) derived from the castor oil plant *Ricinus communis*; it consists of a neutral A-Chain (32 kDa) bound by a disulfide bond to an acidic B-Chain (34 kDa) (Lord et al., 1994). The B-subunit binds to glycoproteins on the surface of epithelial cells, enabling the A-subunit to enter the cell via receptor-mediated endocytosis. This subunit inactivates ribosomal RNA by depurinating a specific ribosomal residue, thereby inhibiting protein synthesis. One ricin molecule can inactivate 2000 ribosomes per minute, which ultimately leads to the death of the cell.

4. Toxicity by ingestion

Ricin is clearly toxic to humans, but the risk will vary depending on the route (and source) of exposure. The dose of ricin required to produce death in 50% of mice (LD_{50}) can be as small as 1–10 μg/kg, when delivered by injection or inhalation (Table 1); lethal doses by ingestion are, however, several orders of magnitude greater. This dramatic difference could in part arise from gastrointestinal digestion and/or relatively low gut absorption of intact ricin. The latter seems a more important factor, as *in vitro* data suggests that ricin is resistant to acidic and proteolytic enzyme degradation (Olsnes et al., 1975) but is poorly absorbed across the intestine (Cook et al., 2006; Ishiguro et al., 1983). This is further supported by the finding that most of the pathology associated with human ingestion relates to local injury predominantly within the gastrointestinal tract, with minimal internal organ injury (Audi et al., 2005; Balint, 1974; Challoner and McCarron, 1990; Lim et al., 2009; Meldrum, 1900; Mouser et al., 2007). Histological studies in rats reveal significant erosion to the intestinal mucosa and evidence of apoptotic cell death (Leek et al., 1989; Sekine et al., 1986). Patients ingesting ricin are susceptible to fluid losses as a direct result of these mucosal injuries; in severe cases, such losses can progress to fatal hypovolemic shock. However, the majority of patients are successfully treated, with a good recovery. Indeed, an exhaustive review of the literature spanning back to the nineteenth century concluded that from a total of 751 cases of ricin toxicity, only 14 deaths were reported (1.9%) (Rauber and Heard, 1985). Of these deaths, 12 occurred prior to 1930, when management of the patient may not necessarily have been as effective.

Nevertheless, the potential exists that ricin could be employed to poison a large urban population. Such a scenario could involve contaminating a regional water supply. To estimate human risks, it is not unreasonable to assume that a dose as low as one hundredth of the mouse oral LD_{50} estimate (of 20 mg/kg) (Bradberry et al., 2003) may be fatal to some susceptible humans. Such an overall "uncertainty factor" of 100 takes into consideration likely inter-species and intra-species variations in humans (IPCS, 1994), and the result equates to a dose of 0.2 mg/kg, or 12 mg in a 60 kg adult for example.

Assuming then that at least 12 mg ricin would be required to achieve lethality in some humans (adults of 60 kg) via the oral route, then, on the basis of an estimated daily water consumption of around 2 l per day, a concentration of 6 mg/l would be required to deliver the necessary dose (at least within a 24 hour period). As an example, the Weir Wood reservoir, which supplies water to approximately 60,000 residents in Sussex, England, has a capacity of 1237 million litres. To achieve the required lethal concentration, approximately 7422 kg of pure ricin powder would need to be introduced to the reservoir. Furthermore, this calculation does not consider the effect of water treatment with hypochlorite, which has been shown to be effective against ricin (Mackinnon and Alderton, 2000). Further variables such as mixing, bacterial degradation, ultra-violet light and other reticulation management practices may also reduce the deliverable concentrations of ricin. Such an exercise, therefore, would be impossible to achieve covertly. Moreover, in the unlikely event of mass poisoning most patients would, with appropriate supportive care, make a full recovery. Lack of mortality in this type of scenario severely limits the feasibility of oral ricin as an agent of mass poisoning.

Terrorists may, however, seek to contaminate water to strategic targets such as houses of parliament or military facilities. These institutions most likely access their water from local government resources and therefore any contamination would be required at points of supply, where security would most likely be greater given their recognised high profile risks, especially since September 11 2001.

To achieve mild morbidity without mortality, such as causing mild gastrointestinal distress within a given population, the amount of ricin necessary to poison a city water supply would be substantially lower. Such estimates are often based on extrapolation from the "no-observed (adverse) effect level" (NOAEL) found from animal studies. To the knowledge of the authors, there are no reported NOAELs for ricin. Nevertheless, it has been proposed, on the basis of theoretical considerations and empirical observations, that the (sub-chronic) NOAEL (at least of biological agents) can be roughly predicted from their acute LD_{50} values (Burrows and Renner, 1999):

$$Sub-chronic\,(\text{oral})\,NOAEL = (0.004/\text{day}) \times (\text{oral})\,LD_{50}.$$

For ricin, with an oral LD_{50} of 20 mg/kg, this equates to 0.08 mg/kg/day. This value can then be used to estimate the likely human no observable adverse effect level (using the same inter- and intra-species safety factors as above), and thence to the likely safe water level, depending on volumes consumed (2 l) and chosen body weight (60 kg). Though there is some degree of imprecision with this model, the

Table 1
Ricin LD_{50} values for mouse via different routes.

Route of entry	Dose to achieve LD_{50} (μg/kg)	Reference
Ingestion	20,000	Bradberry et al. (2003)
Injection	2.8–3.3	Fodstad et al. (1976), Olsnes and Pihl (1973)
Inhalation	1–10	Roy et al. (2003)