

Ricin: Feral Wolf to Hunting Dog!

Ms. Mrinmayee Bhushan

The author is a National Awards winning Techno-entrepreneur; Chevening Rolls Royce Science, Innovation, Policy and Leadership (CRISP) Fellow at Oxford University; Medical Pharmacologist and Microbiologist; and co-founder of Mindfarm Novatech Pvt Ltd, an Indian innovations company.

Summary

Though not considered as effective bioterror agent as either botulinum toxin or anthrax, Ricin is notorious for its perceived potential. This fresh perspective is an effort to analyze the facts related to Ricin, with reference to its newfound therapeutic applications. This big picture should be helpful in understanding the threat in Indian context!

History

Ricin is a protein, naturally synthesized by the castor bean plant. The castor bean contains 3- 5% of Ricin in it. It was discovered by Stillmark first in 1888 as the principal bioactive ingredient of castor bean¹. This is the discovery that led to the birth of Immunology. However, in Ayurveda, there is long history of leaves, roots and beans of the castor plant being used for therapeutic uses, all of which contain varying concentrations of Ricin.

Ricin is one of the most notorious toxins known and is also considered a potential chemical weapon. It features in Chemical Weapons Convention as a placeholder toxin because till date there has been no known peaceful use of Ricin².

However, due to the dark publicity it has received, Ricin has become a popular murder tool not just on TV shows, but also to attempt real life murders by disgruntled wives or to threaten Presidents with laced letters.

Makov and Kostov

It started with the murder of a Bulgarian reporter Georgi Markov in London in 1978 (which has never clinically proved to be Ricin in spite of 30 years of investigation) and attempts to kill Kostov. There are multiple stories and numerous unsuccessful attempts of murder using Ricin and sometimes Abrin too. During the investigations no anti-Ricin antibodies or fool-proof evidence were found in either Markov's or Kostov's blood samples.

Dr. Rufus Crompton, who performed the autopsy on Markov, provided the following explanation for Kostov's survival: "I do not think we really have any idea, except that there is a much bandied about phrase these

days in toxicology: called the 'LD50', which is a dose that will kill 50 per cent of the population. I can only assume that they were working very closely on that” and at the end “circumstantially this was probably Ricin”³.

Toxic

Historically Ricin and Abrin have been extensively researched proteins since 1888 and have been explored for their therapeutic potential as chemo-therapeutic agents.

Though known to be toxic as an aerosol by nasal or intravenous routes of administration, Ricin and Abrin are known to be dermally inactive^{4, 5, 6}. Though known to be toxic, the practical issues related to weaponization of Ricin did not allow it to become a weapon of mass destruction.

Biocrimes or Bioterror?

The exhaustive list of cases involving either confirmed or suspected use of Ricin in a crime, does not involve any incidence of mass bioterror. All cases with confirmed use of Ricin are classified as incidences of biocrimes, challenging the claim of history of use for bioterrorism. When this list of cases is deeply analyzed for the history of possible use of Ricin as a WMD by most feared terrorists groups, there is hardly any substance available⁷.

The fear industry is spending millions of dollars on Ricin-scare⁸ whereas terrorist states and non-state terror groups are using other chemical weapons, planes, cars or lone-wolf attackers to create an impact. There is an urgent need to separate fact from fiction by clearly understanding the fear industry built around the WMD doomsday distractions⁹, because putting these fears in perspective will help us understand this massive focus on bioterror preparedness. Similarly, there is a need to understand the

clear distinction between bio-crimes targeted at individuals and bioterror attacks targeted as weapons of mass destruction.

Due to their hybrid nature, toxins with bioterror potential are either classified as Chemical Weapons or for research, administration and treaty applications as Bio-Weapons¹⁰. For optimizing the threat perception, the non-replicating, non-living, non-transmissible nature of these toxin agents needs to be emphasized.

Fear psychosis

It is interesting to read the suspected origins of anthrax scares post-9/11 and the suspected theft of virulent strains of anthrax spores. There was also a controversy surrounding an anthrax vaccine-making company called Bioprotect and of its investors and networks. The Anthrax scares resulted in a turnaround of an almost bankrupt anthrax antibiotic making company called Bayer¹¹.

With this reference, it is interesting to investigate the clinical progress of Ricin vaccine Rivax and the recent “mix-up” involving use of Ricin during a training program in the Center for Domestic Preparedness (US). The explanation came with a comment saying, “It is worth noting that all of this took place, inexplicably, nearly a month after The Anniston Star first reported that Ricin holotoxin had been used in CDP’s training program¹².

There is always a higher risk of theft of such agents from training facilities which may find their way to the hands of terrorist organizations.

This perspective is vital to decipher complexity of the fear psychosis involved in it and to look at the big picture objectively.

No treatment for Ricin toxicity?

Ricin is a naturally occurring plant-derived protein. There are some treatment options like Lethal Toxin Neutralizing Factor (LTNF) from the opossum serum. It is effective not just for Ricin intoxication but also against a variety of snake venoms, bacterial toxins like Botulinum, scorpions and bee venoms. Such innovations which take inspiration from Nature¹³ such as LTNF, and epigallocatechin gallate from green tea have potential for military applications¹⁴. Similarly, vaccines against Ricin such as Rivax are already under advanced stages of development and Rivax has completed pilot Phase 1B studies^{15, 16}.

Botox and Ricin

Other than Anthrax, one of the most likely biological battlefield threats is the Botulinum toxin. It is the most toxic known natural compound and is way more toxic than Ricin. Ricin is not considered to be as effective as either botulinum toxin or anthrax¹⁷. It is estimated that eight tons of Ricin as an aerosol would be necessary to cause same damage as using only eight kilograms of Botulinum toxin in a given area.

While not many successful botulinum bioterror incidents have occurred around the world, there are examples of unsuccessful attempts to use it as WMD in Japan (1980s) and in Iraq (1991). In spite of all this, scientists envisioned a peaceful therapeutic use of the deadliest toxin known to man and established its image as a glamor drug. And therefore it is not part of the Chemical Weapons Convention (CWC) schedule 1, like Ricin!

Therapeutic use

Ricin has been placed under the 'Schedule 1 of CWC' as a placeholder with an argument

that it does not have any therapeutic value. A scientific publication¹⁸ by our research team challenges even this well-known misconception.

Taking inspiration from therapeutic and commercial success of Botulinum Toxin popularly known as Botox, our research team has developed a breakthrough innovation in an effort to establish the authentic therapeutic and peaceful use of Ricin and Abrin. Ricin and Abrin are historically known to be dermally inactive at high dosage (50 mcg spot). This innovation shows that, at low doses, Ricin and Abrin inhibit the growth of hair follicles¹⁹ by selectively inducing hair follicle dystrophy, without affecting any other skin structures adversely.

After successful preclinical toxicology studies, Ricin and Abrin are now ready for Phase II clinical trials by dermal route.

A clinically tested spin-off cosmetic product of this innovative technology called Romantaque, is already in the market with many happy consumers using it²⁰. This product development was done with Indian Institute of Technology (IIT), Bombay and was funded by Government of India. This patented innovation has won two National Innovation awards in India.

Cytotoxic lectins like Ricin and Abrin have been traditionally considered to be dermally inactive. Their potential to selectively kill cancerous cells has always attracted attention from the scientific community. Phase I clinical trials of Ricin and Abrin have been successfully conducted for chemotherapy applications in 1980s²¹.

With this newfound therapeutic dermal role of Ricin and Abrin, we present a new perspective for the study and peaceful therapeutic use of cytotoxic lectins to the global scientific community.

Indian perspective

India is the largest exporter of castor oil and exports 84% of global requirement of castor oil and its derivatives²². Ricin is part of toxic waste produced by this large industry. However, when we consider it on the research front, pure Ricin, as a protein standard necessary for research, is not commercially available in India. Moreover, there is a ban on export of even 10mg Ricin from the US or Europe. In 2003 the price of pure Ricin as reference protein was INR 13,000/-. With India being the World's largest castor oil industry, when a pharmacologist working in an Indian lab wants to establish the mode of action for an Ayurvedic medicine consisting of castor bean, she/ he cannot get access to pure Ricin as a standard protein. What an irony!

Similar to Ricin related biothreats in other countries; Wipro, a large Indian IT company received a Ricin related biothreat recently²³. Hence, action needs to be taken before it becomes fashionable to use Ricin as a threat in India!

Discussion

The objective of this article is not to discount the potential threat of Ricin, but to endeavor a fresh perspective of looking at a naturally occurring protein.

There is an urgent need to shift the focus from "bio-preparedness" to therapeutics while keeping the bigger picture in mind. This shift needs to occur not just in the scientific community but also in the awareness of the general population. This will help in reducing misconceptions its misuse for biocrimes. These logically flawed adventures not just put tremendous pressure on civic administrations but also create unnecessary fear psychosis in the society. In an era of global information access,

the focus needs to be shifted more towards accurate information which will help in creating awareness and preventing ignorant misuse.

All the arguments of keeping Ricin in Schedule 1 of CWC are moot. Now is the time to revisit this goal-post and eliminate the 'charm' of a cheap WMD from Ricin, and instead position it as a Wonder Drug. This perspective has far reaching research, commercial and strategic implications for India.

Endnotes:

1. Cummings, R. D. & Etzler, M. E. R-type Lectins. in *Essentials of Glycobiology* (eds. Varki, A. et al.) (Cold Spring Harbor Laboratory Press, 2009). <http://www.ncbi.nlm.nih.gov/books/NBK1940/>
2. Medical Aspects of Chemical and Biological Warfare. <http://www.bvsde.paho.org/tutorial1/fulltex/armas/textos/chebio/chebio.pdf>
3. Dr. Rufus Crompton. Georgi Markov- Death in a Pellet. Available at: http://elbdisliker.at.ua/Jedy/Georgi_Markov-Death_in_a_Pellet.pdf
4. David R. Franz,. Defense Against Toxin Weapons. <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.360.3660&rep=rep1&type=pdf>
5. Schep, L. J., Temple, W. A., Butt, G. A. & Beasley, M. D. Ricin as a weapon of mass terror - Separating fact from fiction. *Environ. Int.* 35, 1267-1271 (2009). <http://www.sciencedirect.com/science/article/pii/S0160412009001834>
6. Wannemacher, R.W.; Anderson, J.B. Inhalation Ricin: Aerosol Procedures, Animal Toxicology, and Therapy. In *Inhalation Toxicology*; Salem, H., Katz, S.A., Eds.; CRC Press Taylor & Francis Group: Boca Raton, FL, USA, 2006; pp. 973-982.
7. Bioterrorism and Bio crimes. Available at: <https://fas.org/irp/threat/cbw/carus.pdf>

8. The fear industry. The Washington Times. Available at: www.washingtontimes.com/news/2007/may/5/20070505-101330-9891r/
9. WMD doomsday distractions - Washington Times. Available at: <http://www.washingtontimes.com/news/2005/apr/9/20050409-102738-7969r/>
10. Madsen, J. M. Toxins as weapons of mass destruction. A comparison and contrast with biological-warfare and chemical-warfare agents. Clin. Lab. Med. 21, 593-605 (2001). <http://europepmc.org/abstract/med/11577702>
11. The CIA's Role in the Anthrax Mailings - Could Our Spies be Agents for Military-Industrial Sabotage, Terrorism, and Even Population Control? Available at: http://www.bibliotecapleyades.net/ciencia/ciencia_anthrax-cia.htm
12. House Committee Wants Answers on CDP's Ricin Mixup. Available at: <https://www.printfriendly.com/print?url=uGGCKlrzFJBeyqmpBzlABqrlcbffd>
13. Carmen. Is Tea The Answer To Fighting Bioterror Attacks? | Off The Grid News. Available at: <http://www.offthegridnews.com/misc/is-tea-the-answer-to-fighting-bioterror-attacks/>
14. Lipps, B. V. Anti-lethal Factor from Opossum Serum is a Potent Antidote for Animal, Plant and Bacterial Toxins. J. Venom. Anim. Toxins 5, 56-66 (1999). http://www.scielo.br/scielo.php?script=sci_abstract&pid=S0104-79301999000100005&lng=en&nrm=iso&tng=en
15. Vitetta, E. S. et al. A pilot clinical trial of a recombinant ricin vaccine in normal humans. Proc. Natl. Acad. Sci. U. S. A. 103, 2268-2273 (2006). <http://www.pnas.org/content/103/7/2268>
16. Vitetta, E. S., Smallshaw, J. E. & Schindler, J. Pilot Phase IB Clinical Trial of an Alhydrogel-Adsorbed Recombinant Ricin Vaccine. Clin. Vaccine Immunol. 19, 1697-1699 (2012). <http://cvi.asm.org/content/19/10/1697>
17. Virginia I. Roxas-Duncan & Leonard A. Smith. Ricin Perspective in Bioterrorism. Available at: <http://cdn.intechopen.com/pdfs/33127.pdf>
18. Kondhalkar, M. B., Dr, K. A., Dr, M. W., Paygude, S. & Dr, P. P. Ugly Duckling or a Swan: Exploring therapeutic potential of Ricin for inhibiting unwanted hair growth. Matters 3, e201702000001 (2017). <https://sciencematters.io/articles/201702000001>
19. Kondhalkar M.B. & Parab P.B. 7th World Congress for Hair Research Abstracts. J. Invest. Dermatol. 133, 1391-1439 (2013). #P115 <http://www.nature.com/jid/journal/v133/n5/full/jid2013110a.html>
20. Kondhalkar M., Dudhbhate A., Apte K., Banerjee R. & Parab P. Clinical Study to Evaluate Safety and Efficacy of a Topical Hair Minimizing Lotion in Healthy Human Volunteers. Available at: <http://www.avensonline.org/wp-content/uploads/JCTP-02-0007.pdf>
21. Fodstad, Ø. et al. Phase I Study of the Plant Protein Ricin. Cancer Res. 44, 862-865 (1984). <http://cancerres.aacrjournals.org/content/44/2/862>
22. Castor Oil - It Promises Big Profits [Patience Please!]. Available at: <https://www.thedollarbusiness.com/magazine/castor-oil-it-promises-big-profits-patience-please/32744>
23. Wipro gets second threat mail seeking Rs 500 crore in bitcoin. The New Indian Express Available at: <http://www.newindianexpress.com/cities/bengaluru/2017/jun/02/wipro-gets-second-threat-mail-seeking-rs-500-crore-in-bitcoin-1611926.html>