Is botulinum toxin treatment in children with cerebral palsy really (un)safe?

Reports on adverse reactions of botulinum toxin in children with cerebral palsy raise the risk of over-interpretation, particularly in the context of litigation, warn DMCN readers in response to a recent paper and commentary.

Sir,

We applaud Montastruc et al.’s paper highlighting the importance of reviewing adverse drug reaction (ADR) data. As we interact with families of children with cerebral palsy we each strive to share our understanding of the risk-to-benefit of treatments, especially in children with complex presentation. The article is relevant given the widespread use of botulinum toxin A (BoNT-A), as well as reactive publication of ADR in practice reviews following dose escalation and the boxed warning.

We would like to draw attention to the use of disproportionality analysis and add some clarity to its interpretation. We believe that even when data is presented accurately, we are vulnerable to overinterpretation. Some readers may not be aware that disproportionality tools such as Reporting Odds Ratio are signal detection tools, designed to generate rather than test an hypothesis. Therefore, we felt that the “What this paper adds” bullet point reading “A significant association is suggested between BoNT-A and death in children, but not in adults” may be misleading.

The Reporting Odds Ratio merely indicates that it is possible, because signals should not be taken as causations. As a result, statements about this type of data should be tempered, because of their importance in clinical decision making and litigation, where it might be construed inappropriately as “botulinum neurotoxin is more likely to cause death in children.”

The authors correctly note that there can be no adjustment for the level of disability and pre-existent medical comorbidities of the individual case safety reports (ICSR). Brooks et al.’s review of recent trends in cerebral palsy survival reveals that a child with CP who cannot lift their head in prone, has a gastrostomy tube, and survives to 4 years of age has a 41% chance of survival to 20 years of age. In the absence of information about the levels of function and comorbidities, we must consider that death may be more likely related to these states of health than to BoNT-A, while acknowledging that both may contribute.

Another challenge to interpretation is that reports from providers are voluntary. Death is likely to be reported as an ADR if a drug’s use is temporally linked. Conversely, few epilepsy ADRs were reported despite expected high rates of epilepsy in this population. This likely reflects underreporting because most providers, as the authors expressed, assume it to be an associated condition rather than ADR, implying a risk of failing to recognize a triggered ADR of epilepsy.

We share the authors’ concern of ADR and would support that this signal/hypothesis-generating finding suggests the need for a prospective multi-site surveillance effort of all injections of BoNT-A to identify patient-specific factors and injection parameters associated with safe injections and those more likely to produce ADR. The resulting robust data bank of patient and dosage parameters would enable doctors and families to have a meaningful discussion about risk leading to better informed decision making – even if causation cannot be unquestionably determined.

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REFERENCES


5. Drake v Allergan. District Court of Vermont. 2015. 