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Title

Comments on Miceli Sopo et al.

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Abstract

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Main text

To the Editor,

We read with great interest the paper Miceli Sopo et al.¹ published. The authors described their experience with performing an oral food challenge (OFC) for acute food protein-induced enterocolitis syndrome (FPIES), with a single dose in a full serving size for the age of the culprit food, followed by a 4-hour observation period. The main aim of that study was to assess the safety of their OFC protocol. Indeed, the FPIES international consensus guidelines (ICG)² suggested administering the culprit food at a dose of 0.06 to 0.6 grams per kilogram of body weight (g/kg), divided into 3 equal doses over 30 minutes. However, in clinical practice and in the literature, there are several OFC protocols described³ that deviate from the ICG. In theory, the best FPIES-OFC protocol would be the safest and least time-consuming one.

Miceli Sopo et al.¹ reviewed 222 FPIES-OFCs performed with 91 children. They found 48/222 (21.6%) OFCs failed (positive). Regarding the grade of severity of the failed OFCs, the adverse reactions were predominantly mild or moderate [22/48 (45.8%) and 22/48 (45.8%) of the positive OFCs, respectively], and only 4/48 (8.3%) were severe. They concluded that their protocol was sufficiently safe and had the benefit of saving time.

To compare their findings, in the discussion, they described other published protocols⁴⁻⁷ that guaranteed at least 4 hours of observation between the doses. One of these published protocols has recently been described by our group⁴. We used an OFC protocol consisting of administering 25% of the full culprit food dose (calculated as 0.3 g/kg) and, in the absence of clinical manifestation, the remaining dose 4 hours later, followed by another 4-hour observation. We found 19/54 OFCs (35%) positive with the severity of reactions as follows: 4 (21%) mild, 6 (32%) moderate and 9 (47%) severe.

We were impressed, as Miceli Sopo et al. had been, by the difference in terms of severe reaction rate between the two children populations [4/48 (8.3%) in Miceli Sopo¹ et al. versus 9/19 (47%) in Barni⁴ et al., although these are both Italian studies). As Miceli Sopo et al. did, we wondered about the reason for such a difference.

First, we concluded this finding is not due to a different severity grading system because both works^{1,4} used the one described by the ICG².

Next, we noted that Miceli Sopo et al. found that 2/9 (22.2%) of patients with atypical FPIES had severe reactions in comparison to 2/39 (5.1%) of patients with typical FPIES, so we took into consideration that the reason for the higher rate of severe reaction in our study⁴ could have been due to its having a greater number of patients with atypical FPIES than the Miceli Sopo et al. study¹ had; however, no children in our population had atypical FPIES, so this could not be the reason.

Third, we focused on the children's mean age at which the OFCs were performed. But the ages in both studies were similar (28 months in Miceli Sopo¹ et al. study versus 27 months in Barni⁴ et al. study, respectively); consequently, not even this can be the explanation.

Next, we investigated the time latency between the last FPIES reaction and the performed OFC.

We usually performed the OFC to verify the tolerance to the culprit food 12 to 18 months after the last FPIES reaction, as suggested by ICG², and as soon as possible in case of diagnostic OFC. In our study, the time latency was not specified, whereas in the Miceli Sopo et al. study, it was 6.1 months. Due to the lack of data, this aspect cannot be evaluated.

Then, we studied the percentage of diagnostic OFCs, which were closer to the last FPIES episode in comparison to those performed to verify the acquisition of tolerance. In our study of positive OFCs, 6/19 were diagnostic, and 13/19 were performed to verify the acquisition of tolerance. Regarding the severity of the 6 diagnostic positive OFCs, 1 was mild, 1 was moderate and 4 were severe. Unfortunately, Miceli Sopo et al. study did not specify how many OFCs were diagnostic, so this aspect of the two studies cannot be compared.

Finally, Miceli Sopo et al. speculated that one possible explanation of their lower number of cases with severe reactions might have been due, at least in part, to the timing of ondansetron: In the 17 OFCs in which ondansetron was effective in resolving the clinical manifestations, the drug was administered on average after 2.1 episodes of vomiting, whereas in the 6 OFCs where the ondansetron was not effective, the drug was administered on average after 3.3 episodes of vomiting. Therefore, the authors concluded that the earlier the ondansetron was administered, the more frequently it was successful, and it might interrupt the progression toward a more severe adverse reaction.

The explanation given by the authors does not seem entirely convincing. Indeed, although it is true that our study does not specify the exact time at which the ondansetron was administered—and it is, therefore, not possible to compare this between the two populations—we usually provided the ondansetron immediately after the second vomiting, as suggested by ICG². Furthermore, we administered ondansetron in a greater percentage of failed OFCs in our study than Miceli Sopo et al.: 14/19 (73.7%) versus 23/48 (48%), respectively. In terms of severity of reaction, the ondansetron was administered in 1/2 (50%) versus 12/22 (54%) of mild reactions, 4/6 (66.7%) versus 8/22 (36%) of moderate reactions and 9/9 (100%) versus 3/4 (75%) of severe reactions in our and Miceli Sopo et al. studies, respectively. The efficacy of ondansetron was 12/12 (100%) in mild reactions, 4/8 (50%) in moderate reactions and 1/3 (33%) in severe reactions in Miceli Sopo et al. study. Therefore, considering the timing with which we administered ondansetron and that we administered it in a greater percentage of failed OFCs and in all severe ones, the explanation given by Miceli Sopo et al. about the higher rate of severe reactions in our population does not seem plausible. More extensive data from multicentric cohorts seems needed to confirm that a prompt administration of ondansetron might prevent severe FPIES cases. Finally, our analysis highlights how an international consent on standardized outcomes for FPIES diagnostic procedures appears to be of critical importance to compare the different published experiences in order to establish the best protocol to use.

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