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Pros and Pitfalls of Paediatric Contrast-Enhanced Ultrasound

Despite the widespread use and proven efficacy of ultrasound (US) contrast media in the adult population, as showed in Table 1 (see pg. 39), contrast-enhanced US (CEUS) has not achieved the same level of diffusion in the paediatric population. The rare reports in the scientific literature denote their sporadic and experimental use, most likely in off-label use. Only Levovist® (Bayer-Schering Pharma AG, Germany) is approved for use in children and adolescents and only for the indication of vesico-ureteral reflux study. At the same time production of Levovist® has ceased and it is no longer available. SonoVue® (Bracco Spa, Italy), performs equally well for this particular indication, and for others but it has to be used off-label.

CEUS in Children: Looking Ahead

The current use of CEUS in paediatric work-up in Europe is a sensitive topic. CEUS in paediatric applications remains of critical importance, because of its obvious benefits compared to alternative imaging modalities, which in most cases necessitate exposure to ionising radiation and the use of potentially harmful contrast agents. The benefit of avoiding ionising radiation is clearly far more important in children and adolescents than in adult patients. However the effectiveness and safety of contrast media use in patients <18 years has not been evaluated and their use in these patients is not advisable. There are probably various reasons why US contrast media use in children has not been validated. These include the lower incidence of focal lesions, particularly hepatic lesions in children, and technical reasons: indeed, by using higher frequency transducers, improved sensitivity to vascular flow can be achieved. Then, of course, there are the potential medico-legal consequences in the case of adverse events.

Experimentation with medications in children has always been limited, for two main reasons:

> **Economic:** lack of interest on the part of companies to invest in the paediatric population, which is relatively healthy, with specific studies on efficacy, safety and toxicity.
> **Ethical:** difficulties encountered in subjecting children to the risks involved in experimentation.

Further problems encountered in drug trials in paediatric populations include the tendency to exclude children from phase I trials, with a consequent slowing down of the process as well as;

- The presence of stricter legislation;
- Use of a small patient population;
- Difficulty enrolling children and obtaining an adequate supply of biological samples and,
- The possibility of adverse events that may only become apparent in the long term and therefore go unnoticed unless long-term studies are undertaken.

Currently, the rare reports in the literature concerning such use in children indicate only sporadic and experimental use as shown in Table 2 (see pg. 39). For these reasons US contrast media is currently used in children for off label only, i.e. the use of approved medications for non-approved indications (dose, age, administration route, indications and contraindications) for which the scientific evidence suggests their rational use even in clinical situations not approved by regulations. Moreover there are no specific guidelines available for the off-label use of medications.

The therapeutic activity of the physician is instead currently reputed to be fully legitimate only when the medication has been previously approved by the regulatory body for the same route of administration, dosage or therapeutic indication for which it is effectively prescribed to the patient. In individual cases the physician may, under his [or her] own liability (extended to the head physician when the off-label prescription takes place within a hospital or in the university setting) and after having informed the patient and acquired the patient's consent, use an industrially produced medication for an indication, route of administration, manner of administration or non-approved use. Although it should be noted the formalisation of consent can in no way whatsoever involve mitigation of the level of qualified liability required by the physician, or the acceptance of inadequate treatment or treatment lacking therapeutic justification. There is an apparent need to define requirements, obligations and liability of the physician prescribing off-label medications, in accordance with the laws in force.

The desirable use of contrast media, as in CEUS, even in children, does not imply a decision based on therapeutic need, as the examination is diagnostic in nature and preferable to others that, despite being effective are biologically invasive (the use of ionising radiation, the need for narcosis, etc.). Rather, the diagnostic efficacy of the product and, above all, the scarcity of its side effects provide substantial reasons for supporting the use of this kind of diagnostic instrument both in children and in adults. In this sense, the clear provisions of the Regulation of the European Community No. 1901/2006 dd. 12 December 2006 regarding medications for paediatric use should be followed. With the aim to "facilitate the development and accessibility of medicinal products for use in the paediatric population", the regulation provides for:

- Ongoing improvement of the information available on the use of medications in different paediatric populations;

- Constant updating of analyses on the use of medications in paediatrics, including all forms of off-label use;
- Careful analysis of the existing paediatric medicinal products in order to ascertain the consistency with the favourable scientific evidence in terms of the paediatric risk–benefit profile;
- Standardising, in the setting of a paediatric study framework, indications, dosage, contraindications and precautions for paediatric use of products that contain the same active ingredient.

This regulation undoubtedly indicates a way ahead for safe and certain experimentation that could approve the use of CEUS in paediatric populations and therefore enable the US radiologist to break free from the use of contrast media in an off-label framework.

Conclusions

There is a need to draft new guidelines on the use of CEUS in children to overcome the dichotomy between a strict regulation for an official registration of medical drugs and the absence of specific guidelines available for its off-label use. For these reasons, the physician is on his (or her) own in terms of liability when faced with the decision to use CEUS in children. We are working to assess the efficacy of CEUS in two strands of applicability: trauma and cancer according to the law in force to extend its possible and often decisive use to this category of patients. We are proposing an international working group to bring together the different experiences that can help to draft new guidelines on the use of CEUS in children with the aim to obtain regular use in daily medical practice.

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