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UPDATE IN METHACHOLINE CHALLENGE TEST IN CHILDREN

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ABSTRACT

This document updates the recommendations of the methacholine challenge test in children. It is based primarily on the recommendations contained in the Methacholine Challenge Test Technical Standards Guide from the European Society of Respiratory Diseases. The main change is in the recommendation to use PD20 (methacholine dose that causes a 20% drop in FEV1) instead of PC20 (methacholine concentration that causes a 20% drop in FEV1), which allows for comparable results when using different devices and different protocols.

Keywords: methacholine, asthma, bronchial hyperreactivity

INTRODUCTION

The methacholine challenge test is a nonspecific and direct test, which evaluates the degree of airway reactivity. It is the most appropriate bronchial provocation test in usual clinical practice. Increased bronchial reactivity is a distinctive feature of asthma, but it is also present in other conditions such as bronchopulmonary dysplasia, bronchiectasis, allergic rhinitis, cystic fibrosis, viral infections and also in healthy children. In addition, bronchial reactivity in a patient may change over time, increase in exacerbations, decrease during treatment with anti-inflammatories and be absent in asymptomatic periods (1,2,3). Therefore, the test result must be considered within the context of the patient to be evaluated.

This provocation test is used to assess airway hyperreactivity, which is defined as an increase in sensitivity and exaggerated response to non-allergenic stimuli that cause bronchoconstriction.

It is a support in the diagnosis of bronchial asthma,

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allows to assess its severity, the response to maintenance treatment in the asthmatic child and measures bronchial reactivity in conditions other than asthma.

It has a sensitivity that varies between 80 and 86% and a specificity of 60 to 68% for the diagnosis of asthma, depending on the population analyzed (4,5). In a population with clinical symptoms, the test is highly sensitive, so a normal methacholine test (PC20> 16 mg / ml or PD20> 400 µg) effectively excludes current asthma. Its main indication is to help determine if the current respiratory symptoms are due to asthma or make the unlikely diagnosis in the event that it is negative. Although it is comparable with other pharmacological methods, its use in children is preferred because of its greater technical simplicity and because it has fewer adverse effects. Methacholine is a synthetic derivative of the neurotransmitter acetylcholine that directly stimulates muscarinic receptors on bronchial smooth muscle when inhaled. Methacholine is metabolized by acetylcholinesterase, but more slowly than acetylcholine. Its effects may be partially blocked by anticholinergic agents such as ipratropium bromide.

STANDARDIZATION OF THE TEST

This review is based fundamentally on the recommendations contained in the Methacholine Challenge Test Technical Standards Guide from the European Society of Respiratory Diseases (1).

The age from which a child is able to perform a methacholine test reliably is generally starting at 5. If the young child fails to do FEV1, the response to methacholine can be assessed by measuring Impulse Oscillometry, FEV 0.5, TcPCO2, wheezing auscultation, which is not the objective of this manuscript.

General conditions: the test must be performed one patient at a time and be performed by qualified personnel, trained in this type of examination and experienced in children. The laboratory where the test is performed must have a specialist doctor in charge, responsible for evaluating and verifying the qualification of the technician performing the test. There must be an accessible doctor and resuscitation equipment available.

Before the exam, the nature of the exam should be explained to the caregiver and to the child and it is advisable to have informed consent, signed by the person responsible for the child.

Contraindications: Contraindications for the methacholine test are related to the compromise of the quality of the test or the patient's exposure to a greater risk or discomfort. These are:

- FEV1 <60% of the predicted value
- Inability to perform acceptable and repeatable spirometry maneuvers
- Cardiovascular diseases
- Recent eye surgery or risk of elevated intracranial pressure

Medication Suspension: Patients should receive a list of the medications that should be suspended before the test and their suspension time (Table 1). It is not necessary to discontinue asthma medications other than bronchodilators when the purpose of the test is to evaluate the response to treatment. Antihistamines do not affect the response to methacholine. Inhaled corticosteroids and leukotriene antagonists should not be suspended unless directed by the treating physician. Caffeine and derived products do not influence the test.

The report should record the medications that the patient is receiving at the time of the test.

Table 1. Medication suspension time

Medication	Suspension Time
β agonists short action	6 hours
β agonists long action	36 hours
β agonists ultra-long action	48 hours
Ipratropium bromide	12 hours
Antimuscarinics prolonged action	7 days
Oral theophyllines	12-24 hours

Safety: Inhaled methacholine causes bronchoconstriction. In the design of the work room and in the performance of the procedures, the safety of patients and health personnel must be ensured. The exam room must have adequate ventilation to provide at least two complete air exchanges per hour, to avoid dose accumulation and protect personnel. Preparations with different concentrations of methacholine should be properly labeled and thus avoid inadvertent administration of a high concentration of methacholine. When the fall in FEV1 is less than 20%, the next dose can be administered with little risk of severe bronchoconstriction.

In general, the effects of methacholine are transient and mild, such as wheezing, coughing, dyspnea. A delayed or prolonged bronchoconstrictor response is rare.

A formulation of methacholine available in Chile and

approved by the FDA is Provocholine, which comes in sealed vials of 100 mg lyophilized and dilutions must be prepared by qualified personnel in accordance with manufacturer's instructions. As a diluent, physiological serum can be used. Table 2 shows examples of dilutions for protocols doubling doses or quadrupling doses. The storage of methacholine powder is at room temperature, not more than 25 ° C. The reconstituted solution should be stored between 2 to 8 ° C, with a maximum duration of 2 weeks.

Method: Although PC20 (methacholine concentration that causes a 20% drop in FEV1) is generally used today, the current recommendation is to use PD20 (dose of methacholine that causes a drop in FEV20%). PD20 allows comparable results when different devices and different protocols are used.

Administration devices: Although any nebulizer can be used, it is essential that the manufacturer describe the characteristics necessary for the nebulizer to be used in the methacholine test. Information should be given on the properties and characteristics of the device and the size of particles it grants, to allow the construction of a concentration dose table for the inhalation protocol.

Inhalation protocol: the 1999 guideline (4) suggests that when breathing at a tidal volume the mist should last 2 minutes. The 2017 guideline recommendation (1) states that the time will depend on the performance and characteristics of the nebulizer. The deep breathing method is not recommended because it has a bronchoprotective effect, which reduces the sensitivity of the test.

Provocation dose versus provocation concentration: the dose of methacholine delivered at any level of a provocation protocol is related to the concentration of the administered solution, with the delivery rate of the delivery device, with the inhalation time of the aerosol and with the particle size distribution of the methacholine aerosol, which estimates the fraction supplied to the lower airways. It is feasible to calculate a dose supplied for any combination of device and inhalation protocol. The dose of methacholine, expressed as PD20, allows a more consistent correlation of results than PC20 when comparing the responses made by different protocols. PD20 is the dose of methacholine that causes a 20% drop in FEV1 and is calculated in the same way as PC20. It is recommended to calculate PD20 as the administered dose interpolated between the dose steps before and after a 20% drop in FEV1, regardless of previous cumulative effect. In the case of using the PC20 technique, the nebulizer that will be used in the test must be calibrated to know its debit and ensure that it meets the necessary requirements. After the nebulization with physiological solution, it should be nebulized with increasing concentrations of methacholine, starting with 0.3 mg / ml and doubling the concentration in subsequent doses until obtaining PC20 or reaching 16 mg / ml without PC20.

Execution of the test:

1) Default methacholine concentrations should be prepared in sterile vials and stored in a refrigerator (Table 2). It must be ensured that the spirometer is functioning correctly and that calibration controls have been carried out.

2) Remove the vials from the refrigerator 30 minutes before the test so that the mixtures are at room temperature before use. Introduce an appropriate volume of diluent (3 ml of physiological solution) into the nebulizer, using a sterile syringe.

Table 2. Guidelines for preparing methacholine dilutions

		NaCl (0.9%)	Dilution obtained
Example of dilution guidelines quadrupling concentrations			
100 mg	100 mg	6.25 ml	A: 16 mg/ml
	3 ml dilution A	9 ml	B: 4 mg/ml
	3 ml dilution B	9 ml	C: 1 mg/ml
	3 ml dilution C	9 ml	D: 0.25 mg/ml
	3 ml dilution D	9 ml	E: 0.0625 mg/ml
	3 ml dilution E	9 ml	F: 0.015625 mg/ml
Example of dilution guideline doubling concentrations			
100 mg	100 mg	6.25 ml	A: 16 mg/ml
	3 ml dilution A	9 ml	B: 8 mg/ml
	3 ml dilution B	9 ml	C: 4 mg/ml
	3 ml dilution C	9 ml	D: 2 mg/ml
	3 ml dilution D	9 ml	E: 1 mg/ml
	3 ml dilution E	9 ml	F: 0.5 mg/ml
	3 ml dilution F	9 ml	G: 0.25 mg/ml
	3 ml dilution G	9 ml	H: 0.125 mg/ml
	3 ml dilution H	9 ml	I: 0.0625 mg/ml
	3 ml dilution I	9 ml	J: 0.03125 mg/ml

Using a vial of 100 mg methacholine and NaCl (0.9%) as diluent: The table shows the range of concentrations available to produce appropriate doses using examples doubling dilutions and quadrupling dilutions.

3) Ensure the correct preparation of the patient and perform a spirometry prior to performing the test to confirm that the patient can perform an acceptable and repeatable spirometry, and to determine if the test is contraindicated due to basal bronchial obstruction.

4) Start the test with the diluent using the chosen nebulizer, which will also be used for methacholine solutions. It is recommended to start the test with the nebulization only of the diluent, in particular if this is the first provocation test for the patient and thus ensure that there is no excessive bronchial reactivity. Apply a nose clip and instruct the patient to breathe calmly through the mouth for the appropriate time for the specific nebulizer.

5) Perform post-diluent spirometry at 30 and 90 seconds after the nebulization is complete. After each methacholine nebulization, the decrease in FEV1 should be evaluated in regards to that obtained after nebulizing with diluent, until a 20% drop is observed.

6) The diluent must not cause a significant change in FEV1 prior to testing. If FEV1 has increased or decreased <10% of previous FEV1, proceed to administer the first dose of methacholine. If a ≥20% drop in FEV1 occurs after diluent, the test must be canceled and the patient must be cited for another opportunity. Otherwise start progressive methacholine nebulization. Perform spirometry at 30 and 90 seconds after the nebulization is completed. In order to keep the cumulative effect of methacholine relatively constant, the time interval between two concentrations (from the beginning of a nebulization to the beginning of the next) must be kept constant at 5 minutes using a stopwatch for this effect.

7) At each dose, the highest FEV1 of the acceptable maneuvers is reported.

8) The examination must be suspended in the event of a drop in FEV1 equal to or greater than 20% in regards to the post diluent FEV1 or upon reaching the last established dilution (400 µmol or 16 mg / ml).

9) It is important to consider signs and symptoms of obstruction (coughing wheezing, etc.) that may occur, in which case a fast-acting inhaled bronchodilator must be administered, wait 5-10 min, and repeat the spirometry.

The diluent step is recommended. This allows the patient to be given the opportunity to learn the inhalation technique with the nebulizer and practice in performing spirometry. The clinical significance of a positive response to the diluent is unknown; some patients may be hyper responders to the diluent (saline solution) or they may be experiencing maneuver-induced bronchoconstriction.

Presentation of results: the results are presented as a percentage of decrease in FEV1 in regards to post-diluent FEV1. Data should be presented for each step in the protocol, including post-bronchodilator spirometry.

If FEV1 does not fall at least 20% after the highest dose, then PD20 should be informed as "greater than the final dose given". It should not be extrapolated beyond the last dose. If FEV1 decreases more than 20% after inhalation of the diluent, it should be reported that "There was a significant decrease in FEV1 after inhalation of the diluent and methacholine was not administered."

Interpretation of the bronchial provocation test: it is important to emphasize that more than a given sensitivity or specificity, what the methacholine test does in terms of asthma diagnosis is to change a pretest probability to a posttest probability. This is why the final interpretation of the value of the exam is made by the doctor who attends the patient and requested the exam and is an aid in the diagnostic approach (6).

Table 3 shows the different cut-off points suggested for PD20 and PC20.

It is necessary to note that there is no national or international consensus on the reference values for PC20 or PD20 in children and the cut-off points are arbitrary.

Table 3. Categories of bronchial reactivity to methacholine

PD20 µmol (µg)	PC20 mg/ml	Interpretation
> 2 (> 400)	> 16	Normal
0.5-2,0 (100-400)	4-16	Limit BHR
0.13-0.5 (25-100)	1-4	Mild BHR
0.03-0.13 (6-25)	0.25-1	Moderate BHR
< 0.03 (< 6)	< 0,25	Marked BHR

PD20: dprovocation dose of a 20% drop in FEV1; PC20: provocation concentration causing a 20% drop in FEV1; BHR: bronchial hyperreactivity

CONCLUSIONS

There is no Gold Standard for the diagnosis of asthma, so the performance of the methacholine challenge test has been difficult to establish. The possibility of false negatives due to the protective effect of deep inspirations that prevent the fall of FEV1 or for not having suspended medications for the indicated time should be considered.

The methacholine challenge test is more useful in the exclusion of the diagnosis of asthma than in the establishment of it, because its negative predictive value, when respiratory symptoms are present, is greater than its positive predictive value.

The methacholine challenge test is another element to consider in the diagnostic process of asthma.

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