DMSA provocation test
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Indications

Measurement of mercury concentrations in blood is a useful index of recent exposure to the metal. Urinary excretion of mercury, corrected for urine creatinine and expressed as the molar mercury/creatinine ratio, may also rise after acute and chronic mercury exposure. Hair mercury, which reflects detoxification of the metal from the body, can be used as a longer term indicator of low level mercury exposure; hair mercury levels may rise to concentrations well above the reference interval before there is any clearly defined health effect of mercury accumulation.

However mercury, like other heavy metals, is not well excreted and may accumulate in the tissues to produce chronic adverse health effects without either the blood or urine levels undergoing significant elevation. It is in this situation that a chelation challenge test may be helpful to assess mercury sequestration in the tissues, which can then, in turn, be assumed to be contributing to chronic ill health, including fatigue, anxiety, cardiac effects and elevated blood pressure.

Chelating agents were developed in response to the use of poison gas in World War I. The first widely used chelating agent, dimercaprol (British Anti-Lewisite, BAL) was used as an antidote to the arsenic-based poison gas, Lewisite. BAL was modified into DMSA (meso 2,3-dimercaptosuccinic acid), also known as "succimer", in the 1960's, to give a di-thiol compound with fewer side effects [1]. DMSA is a sulphydryl-containing, water soluble, orally administered chelating agent which can be used can be used in a chelation challenge test [2,3,4] although its primary use is in the treatment of metal toxicity, rather than its diagnosis. DMSA was originally approved for use in the treatment of paediatric lead toxicity [5,6,7].

DMSA can be used to extract other metals, such as arsenic, lead, and thallium from the tissues. It also chelates aluminium, antimony, cadmium, chromium, cobalt, copper, manganese, selenium, and zinc [Biolab Medical Unit, unpublished results]. DMSA is not thought to cross the blood brain barrier in humans, so will not directly remove metals sequestered in the central nervous system [1].

While our experience at Biolab suggests that the DMSA provocation tests often yields informative results, including negative results which can be used to exclude chronic mercury toxicity, there is, however, no clearly defined index of normality and the results may need careful interpretation.

Principle of the test

Excess mercury in the tissues is tightly bound to sulphur-containing amino acids and normally poorly excreted into the urine. The oral administration of 15 mg of DMSA per kg body weight is used to provoke the release and excretion of mercury; subjects with excess tissue storage of mercury will at least double their urine concentration of the metal over a 2½ hour period post oral DMSA. In the absence of excess metal sequestration no significant increase in urinary mercury excretion will be observed.

DMSA will also chelate other heavy metals, so while this is primarily used as a challenge test for mercury overload, other toxic metals can also be usefully measured in the urine samples provided.

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Safety

The use of DMSA in women who are pregnant or breast feeding is absolutely contraindicated [8].

Biolab does not take responsibility for clinical reactions which may result from the use of this agent. Such reactions are rare and are thought to be related to the mobilisation of mercury from the tissues into the vascular circulation. DMSA should therefore not be administered to subjects with known or suspected white cell sensitivity to metals. Additional idiosyncratic reactions, such as skin rashes and mild neutropenia are also a possibility. One disadvantage of the use of DMSA is its ability to mobilise cadmium, which can be nephrotoxic, so a further contraindication to its use is the presence of cadmium toxicity or renal dysfunction.

DMSA may impart an unusual smell to the freshly-voided urine. This is not part of a toxic reaction to the chelating agent.

In spite of these necessary caveats, DMSA is a safe and widely used agent. For example, technetium-99m DMSA scintigraphy is the radiological method of choice for the detection of acute infections and chronic renal lesions in children [9]. Biolab has reported on many thousands of DMSA provocation tests which have been carried out without reported side effects [10].

DMSA dosage

DMSA is supplied in capsule form and the number of capsules used should be calculated from the DMSA content of the capsule (e.g. 100 mg) and the patient's body weight. It is recommended that the DMSA used for the provocation test should be taken on its own, without co-adminstration of other chelating agents and not in a mixed preparation with micronutrients (such as ascorbic acid or glycine).

We have found that a DMSA dosage of 15 mg/Kg body weight is the most useful to distinguish subjects with excess mercury from subjects with "normal background exposure" to mercury. The use of higher doses of DMSA does not improve this distinction.

Children under 16 years of age having the test should receive 10 mg DMSA/Kg body weight [11].

Patient preparation

The patient can eat and drink normally (but not excessively) during this test, which can be carried out at home. The dosage of DMSA used should be calculated from the subject's current body weight.

Specimen requirements

The patient should provide two separate random urine samples, the first one immediately before taking DMSA and the second 2½ hours (150 minutes) after taking the capsules. Any urine produced in between should be discarded. The patient may drink in moderation and urinate during the course of the test without the result being affected. The two samples should be sent to Biolab for analysis without delay.

Maximum urinary production of metals is reached at around 2½ hours post DMSA, but there is no clear peak of excretion.

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Methodology

Urine mercury and other metals are measured by inductively coupled plasma – mass spectrometry (ICPMS) and urine creatinine by a colorimetric Jaffe method. The results are expressed as the molar metal:creatinine ratio, to correct for variations in urine dilution.

Turnaround time: 5 working days.

Interpretation

Mercury is a toxic metal with no known biological essentiality in man and its presence in any concentration can be regarded as harmful under certain circumstances.

There is no clearly defined reference interval for the increment in mercury production post DMSA; ideally the molar mercury/creatinine ratio in the basal sample should be less than 0.50, while that in the DMSA-provoked sample should be less than 1.00. The reference interval quoted on the report for the basal urine mercury/creatinine ratio (less than 2.00) reflects the current excessive dietary and environmental intake of mercury in this population.

However, a "normal" DMSA provocation test result (i.e. no excessive body mercury present) can be taken as an increase in urine mercury (corrected for creatinine concentration) of less than 100 % (= twice the initial value) and below 2.00 μmol Hg per mole of of creatinine.

Co-administration of chelating agents and other substances promoting metal excretion will influence the results of the DMSA provocation test, principally to raise the basal mercury/creatinine ratio and blunt the response to DMSA.

References:

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