

Minimising Harm from Newborn Screening Programmes

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Abstract

The challenge of newborn screening programmes is to maximise benefits and minimise harms. These harms include pain inflicted as a result of taking the test, reduced by pain relief and training of specimen takers; from false positive and negative test results (impacting both affected families and healthcare professionals), minimised effectively by taking the sample at the correct time, precise and specific tests, appropriate disorder definition, well chosen cut-offs (which may be informed by a large series of diagnosed cases of the screened disorders) second-tier tests, age adjusted normal ranges and anxiety which may be appropriate but limited by the availability of information. Programme audit is important in early detection of problems.

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Introduction

Newborn baby metabolic screening programmes are public health programmes which minimise the morbidity and mortality from inborn errors of metabolism. However, these inborn errors of metabolism are rare conditions and relatively few babies get significant benefits from the screening programme while there is the potential for many more to be harmed, albeit in a minor way. The screening programme has components of sampling, laboratory testing, repeat and diagnostic testing, treatment, policy/planning; funding, and audit. Each of these components can impact adversely on both affected and unaffected infants.

Method

Components of a typical newborn baby metabolic screening programme were examined for negative impacts on affected and unaffected infants, and for strategies for minimising the negative impacts.

Results

Figure 1 shows the interrelation of the different screening programme components. The likely harms resulted from the components include the following.

Policy and Planning – Test Cut-offs

Setting test cut-offs must take into account also the true biological value and the imprecision of the test at that level to ensure all infants with values at the cut-off are recalled. Assays using blood dried on paper are inherently less

precise than the equivalent serum tests which must be taken into account. Improvement of assay performance so the test has minimum variation around the cut-off means less both false positive and false negative results. There must be understanding of assay bias if comparing with literature and other programmes and use of the International Society for Neonatal Screening (ISNS) minimum dataset and kits calibrated against ISNS reference materials¹ can assist harmonisation. Each local programme needs to make value judgements of the cost of additional recalls against the benefits of finding additional, probably mild cases of screened disorders. Additional specificity can be gained by using cut-offs varied with infant maturity and age at specimen collection.²

It has been suggested³ that disorder cut-offs are defined by the use of large studies combining all the positive tests from many screening programmes rather than by using statistically determined cut-offs. This is a commendable approach (historically well used by screening programmes but without the benefit of large case numbers obtainable by world-wide collaboration) but may need modification to take into account disease severity and timing of sample.

All positive tests rightly generate anxiety in families and it is proper that programmes seek to minimise this. The anxiety however may be appropriate and short-lived⁴ but over the screened community early detection may minimise anxiety and the stress of caring for affected, untreated children. False alarms cause desensitisation of laboratory and follow up personnel which may result in failure to take

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appropriate speedy action when a true case presents. False positive tests can result in the expense and inconvenience of unnecessary treatment unless they are followed by appropriate diagnostic tests.

False negative tests impact on those with the disorder and with screening programme credibility. There are those which are unavoidable (screening marker not raised, or not reliably raised at the time of testing e.g. blood glycine in non-ketotic hyperglycinemia, immunoreactive trypsin in cystic fibrosis screening); and those which are avoidable due to programme failures. False negative tests can be minimised by good laboratory practices.⁵ Greater clarity of disorder definition and of community expectations can minimise the impact of false negative test results.

Sample Collection

It is now recognised that neonates feel pain, including that from medically induced procedures. All affected and unaffected infants will be inflicted. Recent recommendations from the Royal Australasian College of Physicians Paediatrics and Child Health Division for minimisation⁶ include:

- Do not warm the heels of the neonates as this does not reduce pain or aid blood collection
- Consider use of oral sucrose (0.5-1 mL 24%, 2 min before)
- Encourage breast or bottle feeding
- Ensure parent or carer holds baby
- Use automated retractable lancet

Samples sometimes cannot give reliable test results when they are badly collected perhaps due to insufficient blood collected, layered blood, spills etc, or because they are not taken at a time for which the programme has validated cut-offs. Or because the analyte of interest is not abnormal at that time e.g. samples taken are too early for detection of amino acid disorders. A recent study testing pairs of satisfactory and unsatisfactory portions of the same sample showed both low and high bias depending on the cause of the inadequacy giving increased false positive or negative tests depending on the disorder. Samples collected too early may give false positive screens for congenital hypothyroidism, cystic fibrosis and congenital adrenal hyperplasia, and false negative for amino acid and fatty acid oxidation disorders. Unless age-adjusted normal ranges are used, samples collected too late can also give false negative results for cystic fibrosis and fatty acid oxidation disorders. Strategies for minimisation are training and education of specimen collectors and laboratory assessment of the effects of the particular problem with the sample and accepting a result which may be quantitatively inaccurate but in screening terms an accurate result. Delays in sending samples can also produce harm from delayed diagnoses,

minimised by collector education and provision of courier or stamped envelopes.

Policy and Planning – Disorder definition

The decision limit for a positive test impacts both false positive and false negative test numbers. First, the disorder must be defined, taking into account that while these conditions are monogenic they present in a spectrum of disease (“metabolome”) and the mild end of the spectrum may not have significant clinical benefit from early diagnosis. The Australasian programmes have begun to define conditions e.g. cystic fibrosis, “Cystic fibrosis (CF): Patient with one or more characteristic phenotypic features (including meconium ileus); or a history of CF in a sibling; or a positive newborn screening result AND 2 CFTR disease-causing mutations or a sweat chloride concentration greater than 35 mmol/L”. The aim of definitions like these is to enable screening programmes to determine programme metrics in a timely manner, to reduce false positive tests and to exclude as a screening objective detection of e.g. CF so mild that it presents as cough or infertility in older adults.

Laboratory Testing

Newborn screening laboratories typically test large numbers of samples of which a low proportion have positive tests and a lower proportion are affected by the screened condition. It is too easy for lack of attention to lead to muddled samples and screening laboratories lack the benefit of past history clinical laboratories have to aid in detection of this type of error. The typical screening programme has a large number of repetitive action involved in punching and testing samples which put staff at risk from overuse and pain syndromes. Development of more automated testing systems minimises both human errors and risk of occupational health harms.

An important strategy for improving specificity one is the use of more specific first line testing for example use of immunoassays with more specific antibodies, analyte ratios such as phe/tyr to improve PKU screening. Second tier tests such as succinylacetone in tyrosinemia screening, phe/tyr ratio in PKU screening, specific 17-hydroxyprogesterone or steroid profiles in CAH screening have proven benefits on test specificity.⁷

Treatment

Potential harm resulting from unnecessary or inappropriate treatment can be minimised by the use of confirmation before treatment (e.g. screening test plus appropriate clinical symptoms, screening test plus diagnostic test). Complete diagnostic test algorithms are available (the American College of Medical Genetics - ACMG ACT sheets).⁸ Ongoing involvement of local specialist paediatricians is important to ensure locally appropriate,



Fig. 1. Interaction of screening programme components.

up-to-date protocols for repeat testing following screen-positive results are available.

Programme Audit

Programme audit is critically important in recognising and solving problems which can arise from changed circumstances e.g. kit antibodies, laboratory information systems programming, locally changed specimen collection practices. Such things as recall rates for the different screening tests, coverage, sensitivity, specificity and positive predictive value of the different tests could be monitored. Programme audit must inform programme policy.

Discussion

All newborn metabolic screening programmes do a lot of good, and all do some harm. The programme challenge is to maximise the former while minimising the latter. Screening programme components other than those above can also affect outcomes, e.g. insufficient funding and uninterested government departments. Most programmes

have laboratory funding but not specimen collection, diagnosis and treatment funding from the same source, which creates difficulties in programme management. The strategies for minimisation of harm discussed above are primarily those from the part of the programme most easily managed, the laboratory.

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