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能測定新生兒的總氮含量嗎?

Can total body nitrogen be measured in newborn infants?

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The feasibility of using prompt in vivo neutron activation Analysis (IVNAA) of nitrogen to measure the total body nitrogen (TBN) of newborn infants has been investigated by redesigning and recalibrating an existing IVNAA facility used for the measurement of TBN in adults. Repeated 1000 sec measurements of an infant phantom (4kg wt: 80g N) yielded an average measured value that is within 0.2±1.8% (1xSD) of the actual value and a precision of 7.9% (CV) for a single measurement. Preliminary investigations indicate that the whole body radiation dose is no greater than 1 mSv (Q=20) for a 1000 s irradiation. It is proposed, and in part demonstrated, that measurement precision can be reduced to ≈5% by (i) using a graphite neutron reflector positioned over the infant to increase the in vivo thermal neutron flux, and (ii) doubling the number of NaI(TI) detectors.

Introduction

There is increasing evidence to suggest that total body nitrogen (TBN) is an important indicator of nutritional status in health and disease[1], nitrogen being related to protein by a relatively fixed ratio of 1:6.25. Although several clinical centres have established non invasive methods of measuring TBN in adults[2-5] and children[6-7], no method has been routinely applied to measure the TBN of newborn infants[8]. If this could be achieved, it would contribute significantly to the early diagnosis and effective management of diseases affecting protein stores during the most formative period of growth, increasing the likelihood of a favourable prognosis.

At present in vivo neutron activation analysis (IVNAA) is the only non-invasive method for the in vivo measurement of TBN. In the prompt γ-IVNAA method the subject is irradiated with fast neutrons which are subsequently moderated within the patient and then captured by nitrogen nuclei according to the reaction $^{14}N(n,\gamma)^{15}N$. The prompt γ-ray released in this reaction has a characteristic energy of 10.83 MeV and can be identified and counted by NaI detectors. The number measured over a 1000 s period will be referred to as the signal (S) where it is assumed that S is proportional to the mass of nitrogen irradiated. The gross signal coming from the detectors contains a background (B) component which must be measured separately and then subtracted to obtain S.

This method is routinely applied to adults at the Monash Medical Centre (MMC). In particular, a collimated neutron beam (20 cm x 40 cm at bed level) from a 10 μg ^{252}Cf source (2nd July, 1992) unilaterally irradiates the trunk section of a static subject for 1000 s whilst two 10 cm x 10 cm x 15 cm NaI(TI) detectors positioned bilaterally 50 cm apart measure S with a precision of ≈ 4% from an effective radiation dose of 0.4 mSv (Q=20)[9].

If this method for adults were applied to infants, the measurement precision would be unsatisfactory. To illustrate, consider the standard man weighing 70 kg and containing 1800 g of nitrogen[10]. Only half of this nitrogen mass, ie 900 g, is irradiated. The gross counts from an adult measurement is 2800 with a background of approximately 900 per 1000 s. However, an infant is assumed to weigh 4 kg, 80 g of which is nitrogen[10]. Hence the nitrogen counts from an infant would be reduced by a factor of ten because the quantity of nitrogen being irradiated is approximately one-tenth of that in the adult (ie 80 g compared with 900 g). For an infant measurement, B would remain at about 900 counts but the gross counts would be 990 (ie 900 + 0.1 [2800–900]) which would give a measurement precision[11] of 48% for S. This could be improved by counting for a longer period of time, but this would increase the radiation dose to the infant.

In view of these difficulties, a study was conducted to determine whether the MMC IVNAA facility could be redesigned and calibrated to measure the TBN of infants with a precision of ≈5% and a radiation dose comparable to that for adults. This study follows the work of Wang et al.[8] which considered the measurement of various small animals. Although no infants were measured, these works demonstrate the potential for the measurement criteria of this study to be met.

Design study of the IVNAA facility

Figure 1 is a cross-sectional view of the infant IVNAA facility. The design aims were to (1) maximize S, which is proportional to the in vivo thermal neutron flux and the detection efficiency for 10.83 MeV γ-rays, and (2) to minimize B. Signal was optimized by investigating: (1) the neutron collimator composition and geometry, (2) the number and positioning of NaI(Tl) detectors, (3) the use of a fast neutron pre-moderator inserted between the neutron source and the subject, and (4) the use of graphite positioned above the subject to reflect leaked neutrons back into the subject.

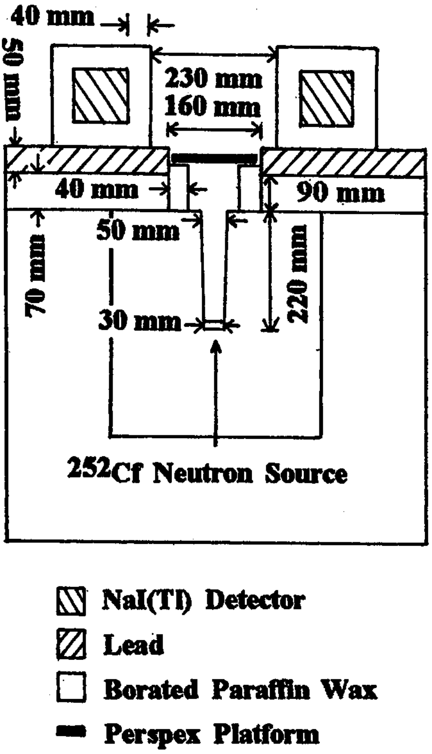

Figure 1. Cross sectional view of the IVNAA facility for the measurement of TBN in newborn infants.

Background was reduced by investigating: (1) neutron collimator geometry and (2) neutron and γ-ray shielding composition and geometry.

Signal maximization

The ^{252}Cf source is positioned at the apex of an inverted rectangular conical void cast within a paraffin wax block (40 cm x 40 cm x 60 cm) doped with boric acid (H_3BO_3, ≈5% wt). The size of the neutron beam exiting the collimator is defined by an aperture measuring 5 cm x 30 cm. A narrow aperture width increases the proportion of slow neutrons in the neutron beam and reduces the dose to the patient[12,13] whilst the aperture length ensures maximum exposure along the subject. A narrow neutron beam also makes possible the reduction in separation of the NaI detectors from 50 to 25 cm without substantially increasing B; this increases the geometrical detector efficiency by a factor of four according to the inverse square law. Two additional NaI(Tl) detectors of equal volume are awaiting installation; this will increase S by a further factor of two.

The effects of a pre-moderator were studied by inserting a 2 cm thick paraffin wax block between the ^{252}Cf source and subject and performing 1000 s counts on calibration phantoms. Results are shown in Table 1. It was expected that this would increase the thermal neutron flux within the nitrogen phantom and hence increase S. The experiment resulted in a significant reduction in S (≈11%) and a somewhat less significant increase in B, demonstrating that the effect of a pre-moderator can be quite complex (see Table 1).

Unilateral irradiation results in a significant proportion of neutrons passing through the subject. In a final set of measurements, a graphite slab was placed above the phantom to determine if these neutrons could be reflected back into the phantom and increase S relative to B. This was tested using a 15 cm x 5 cm x 40 cm graphite slab positioned ≈5 cm directly over the infant phantom. Results are shown in Table 2 for a 1000 s irradiation. A statistically significant increase in S was noted, leading to an improved precision. Stamatelatos[14] has investigated this effect in some detail and reported results that support this observation.

Table 1. Effect of a 2 cm wax premoderator on the measured value of S.

	Signal (S)	Background (B)
No wax premoderator	1544±54	713±27
Wax premoderator	1372±54	763±27

Table 2. Effect of a graphite reflector positioned above the infant phantom.

	No Graphite Reflector	Graphite Reflector
Signal (S) ± statistical error (σ)	474±36	639±38
Background (B) ± statistical error (σ)	790±28	808±28
σ/S x 100%	9.6%	7.4%

Background minimization

The major background component of a γ-ray spectrum (B) arises from the interaction of neutrons and γ-rays with the NaI(Tl) crystal[11]. Although detection of B is unavoidable, the geometry and composition of shielding materials have been designed to minimize B.

Borated paraffin wax above the neutron collimator moderates and captures leaked neutrons and a 5 cm thick lead shield absorbs γ and neutron radiation. The narrow collimator directs the neutron beam away from the detectors and onto the subject.

Calibration of TBN measurement

Body hydrogen is used as an internal standard when measuring nitrogen[15]; this is implemented by counting the prolific 2.22 MeV γ-rays arising from neutron capture in body hydrogen. Subject measurements are calibrated against a phantom of similar shape and size containing a known mass of hydrogen and nitrogen. The background in the 10.83 MeV region of the γ-ray spectrum (nitrogen background [NB]) is determined using a plain water phantom. Background in the 2.22 MeV region (hydrogen background [HB]) is determined with no phantom positioned above the neutron source (ie 'air phantom').

In particular, it is difficult to determine HB. This is because a significant proportion of HB arises from the subject reflecting neutrons into the collimator and shielding materials where ^{1}H nuclei are subsequently activated; this effect varies with subject size[16]. Table 3 presents results of measurements that have been performed on two different phantoms to determine HB. The results demonstrate that HB has the potential to significantly affect the determination of the subject's hydrogen count rate because HB is so large. However, the

Table 3. Measured estimates of the hydrogen background (HB).

	Infant phantom (4 kg Urea solution:80g N)	Air phantom	Graphite Phantom ($15x5x40\ cm^3$)
Total H counts (S+B)	1 962 725		
Measured ^{1}H B		701 226	799 150
Measured ^{1}H B as % of total ^{1}H counts of IP[a]		35.7%	40.7%

[a] Infant phantom

Table 4. Nitrogen measurements of an infant phantom and a sample of minced beef.

Phantom type	Mass (g)	No. of independent measurements	Actual N mass (g)	Measured N mass(g)	CV
Urea solution	4000	20	80.0±0.2	80.1±6.4	7.9%
Minced beef	3000	7	unknown	92.4±3.7	4.0%

observed 15% difference in HB translates into a systematic error of only 1.1% when calculating TBN. This insensitivity arises because TBN depends on the ratio of two hydrogen count rates (phantom/subject) and this ratio is less sensitive to the value of HB. Although this does not dismiss the need to carefully quantify the effect of varying subject dimensions, for the purpose of this study, air phantom measurements with a +15% correction were used to estimate HB.

Results of accuracy and precision measurements

Methodological accuracy and precision were determined from 20 1000 s exposures of a 4 kg infant phantom (16 cm x 8 cm x 38 cm) filled with urea solution containing 80 g of nitrogen. The precision of measuring a 3 kg sample of minced beef was also determined[8]. Every measurement was independently calibrated against a calibration phantom where no graphite reflector was used. Table 4 details the results.

The actual nitrogen content of the infant phantom is within 0.2% of the average measured value and within the associated error range predicted by nuclear statistics (±1.8% SD); this suggests the accuracy of the method to be better than ≈98%. Reproducibility measurements of the infant phantom suggest the precision of the method to be 7.9% (CV); this agrees with the ≈10% value predicted by nuclear statistics.

The measured nitrogen content of the beef sample is consistent with similar measurements performed elsewhere[8] and with the expectation that an increased nitrogen content results in an increased measurement precision.

Dosimetry

The radiation dose to the subject arises from neutrons and γ-radiation, fast neutrons being the major dose component[13]. The dose equivalent was measured at both the anterior and posterior surface of the infant phantom using standard personnel radiation dosimeters[17]. A conservative calculation of the effective dose equivalent to the whole body was then performed with the infant assumed lying supine. This preliminary investigation yielded an upper limit of 1 mSv (Q=20); no graphite reflector was considered. This value compares to a newborn infant chest X-ray effective dose equivalent of 0.1 mSv. Dose measurements have not yet been performed with the graphite reflector in position.

Discussion

This study demonstrates that prompt IVNAA can be used to measure the TBN of newborn infants (≈ 4 kg mass) with a precision of 7.9% and an accuracy better than 98% for an effective dose equivalent value to the whole body no greater than 1 mSv (Q=20). If the number of detectors are doubled and a graphite neutron reflector positioned above the subject, the measurement precision is expected to decrease from ≈10% to ≈5% making the method useful in clinical applications.

Further work is required to quantify the calibration procedure for subjects of varying dimensions. More importantly, an accurate measurement and calculation of the radiation dose is required to establish the level of health risk to which the subject is exposed. However, it is encouraging to note that the effective dose equivalent estimated in this study is at most 1 mSv. This order of exposure has been classed by the ICRP to represent a minor level of health risk and would be justified if the experiment produces a health benefit[18].

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