URINARY EXCRETION AND METABOLISM OF PETHIDINE AND NORPETHIDINE IN THE NEWBORN

M. I. J. HOGG, P. C. WIENER, M. ROSEN AND W. W. MAPLESON

SUMMARY
In seven neonates, whose mothers were given pethidine during labour, urine was collected for the first 24–40 h of life. Urinary volume and pH, and concentrations of pethidine and norpethidine in the urine were measured. Urine flow rate was low for the first 7–22 h, and then high for about 12 h. The rate of excretion of pethidine and norpethidine was approximately parallel to the urine flow rate. However, the ratio of the rate of excretion of norpethidine to that of pethidine increased with time and the concentration of norpethidine in urine decreased first and then, after 18 h, increased significantly. These findings indicate that the neonate can metabolize pethidine, although the rate of metabolism is probably less than in the adult. The total amounts of pethidine and norpethidine excreted in the first 24 h after birth were positively related to the dose–delivery interval in the mother for intervals up to at least 5 h. From the data it is estimated that 95% of the total pethidine transferred from the mother would be eliminated by the baby by the 2nd to 3rd day after birth.

Pethidine produces respiratory depression in the neonate (Koch and Wendel, 1968) and changes in behaviour which may be discernible for days (Brackbill et al., 1974; Wiener, Hogg and Rosen, 1977a, b) or even weeks (Richards and Bernal, 1972). This seems surprising since the pharmacological effects of pethidine would not be expected to last so long; however, there are no data available on the rate of excretion of pethidine in the neonate. This information could have practical importance when deciding, for instance, whether or not to repeat the dose of a narcotic antagonist in a neonate.

Although pethidine and its metabolites, transferred from the mother, appear in neonatal urine (Way et al., 1949; Crawford and Rudofsky, 1965; O'Donoghue, 1968, 1971) the evidence for metabolism of pethidine by the neonate is contradictory: Crawford and Rudofsky (1965) failed to demonstrate metabolism in two babies given pethidine i.m.; O'Donoghue (1968) did demonstrate metabolism but in one baby only. Consequently, the excretion kinetics of pethidine and norpethidine have been measured in the newborn, from birth, following the administration of pethidine to the mother during labour.

METHODS
Babies of 37 mothers who had received pethidine during the first stage of labour were studied. However, the practical difficulties of collecting urine were such that complete collections were obtained from only seven babies. All the neonates were delivered by the vertex, either spontaneously or easily by forceps, and had an Apgar score greater than 7 at 1 min. At delivery, maternal venous blood and umbilical venous blood were taken for measurement of pethidine concentration in plasma.

Urine was collected using a Hollister newborn U-bag attached for up to 48 h after birth. The bag was fitted as soon as practicable after birth and careful observation made it almost certain that no urine was passed between birth and the fitting of the bag. During the collection period the bag was inspected frequently by one of a team of nurses employed for the study; if a leak was found or even suspected in the bag attached to any baby, that baby was excluded from the study. Urine was removed from the bag using a sterile 10-ml syringe and the volume was recorded. The time was noted when the bag was emptied, the urine pH recorded and the sample stored at −24 °C. Each urine specimen was analysed for pethidine and norpethidine concentration by gas chromatography. The method used was a modification of that of Taylor (1968) and in our hands it had a coefficient of variation for pethidine in urine of 4.6% at 0.8 nmol. ml⁻¹ and for norpethidine in urine of 12.7% at 1.9 nmol. ml⁻¹.

RESULTS
All the neonates were male. Table I summarizes some of their characteristics. Five mothers had been
Table I. Maternal pethidine dose, plasma concentrations at delivery, birth weight, urine pH and timing of urine collections in seven neonates

<table>
<thead>
<tr>
<th>Subject</th>
<th>Maternal pethidine dose (mmol)</th>
<th>Dose-delivery interval (h)</th>
<th>Birth weight (kg)</th>
<th>Pethidine plasma concn (nmol ml⁻¹)</th>
<th>Mean urine pH</th>
<th>Delivery to start urine collection (h)</th>
<th>Start to last collection (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>0.455</strong> i.v.</td>
<td>—</td>
<td>3.50</td>
<td>0.93 0.93 1.00</td>
<td>7.2</td>
<td>0.85 38.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.529 i.m.</td>
<td>1.83</td>
<td>2.90</td>
<td>3.07 2.02 0.66</td>
<td>7.0</td>
<td>0.83 39.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><strong>0.705</strong> i.v.</td>
<td>—</td>
<td>3.29</td>
<td>2.22 1.50 0.67</td>
<td>—</td>
<td>1.00 30.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.352 i.v.</td>
<td>—</td>
<td>3.44</td>
<td>0.73 0.73 1.00</td>
<td>—</td>
<td>0.85 47.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.529 i.m.</td>
<td>2.65</td>
<td>3.33</td>
<td>1.74 1.33 0.77</td>
<td>7.2</td>
<td>0.70 23.8</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.529 i.m.</td>
<td>5.03</td>
<td>3.94</td>
<td>1.54 2.14 1.40</td>
<td>6.2</td>
<td>1.25 42.8</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.529 i.m.</td>
<td>5.17</td>
<td>3.61</td>
<td>1.78 1.58 0.89</td>
<td>6.1</td>
<td>0.88 41.3</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.518</td>
<td>3.30</td>
<td>3.43</td>
<td>1.70 1.45 0.91</td>
<td>6.77</td>
<td>0.91 37.6</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>0.106</td>
<td>1.68</td>
<td>0.32</td>
<td>0.81 0.53 0.26</td>
<td>0.49</td>
<td>0.17 8.0</td>
<td></td>
</tr>
</tbody>
</table>

* Total dose of i.v. pethidine by patient demand.
† MV = maternal venous; UV = umbilical venous.

Given pethidine by i.m. injection and the other two used a slow-i.v.-injection self-administration method (Evans et al., 1976). The doses of pethidine, the dose-delivery intervals and the neonatal birth weights were typical of those in this hospital (Evans et al., 1976). Maternal and umbilical plasma concentrations of pethidine and the umbilical/maternal ratio were similar to those in other reports (O'Donoghue, 1968; Taylor, 1968). Mean urine pH was slightly acidic. (Fluctuations within each neonate were small.) With this small group of neonates no relationship was apparent between any of the measured variables and the dose of pethidine or the dose-delivery interval except for a suggestion that long intervals were associated with more-acid urine.

In all instances urine collection was started within 1.25 h after birth. In adult studies the times of collection of urine are the times of micturition; but to have made collections at micturition in the neonate would have necessitated continuous observation of the collection bag. In order to approach this ideal the bag was inspected at frequent, usually half-hourly, intervals. For each emptying of the collection bag the volume of urine it contained, and the amounts of pethidine and norpethidine therein, were divided by the time since the last emptying (the "collection period") to yield rates of excretion.

Since the collection periods varied, the following procedure was adopted to derive average excretion rates. For each neonate cumulative excretions of pethidine, norpethidine and urine were plotted against time from fitting the collecting bag (for example fig. 1). Assuming that in a collection period the rate of excretion is constant, each consecutive pair of points can be joined by a straight line. At any time, therefore, the amount of urine excreted can be estimated from the graph. For instance, in the interval...
18–21 h, 17.2 ml of urine is the estimated excretion, giving a mean rate of excretion for that 3-h period of 5.7 ml h⁻¹.

For each neonate, the rates of excretion of urine, pethidine and norpethidine, averaged over each 3-h period, were derived in this manner and then averaged over the group. From these rates the cumulative excretions and the average concentrations (for each 3-h period) of pethidine and norpethidine were derived for each individual and then these also, with the corresponding rates of excretion, were averaged over the group. The rates of excretion of urine, pethidine and norpethidine are plotted against time from fitting the collecting bag for a typical individual in figure 2 and for the average neonate in figure 3. In both figures there is a remarkable parallelism between the rates of excretion of pethidine and norpethidine on the one hand and that of urine on the other. Usually for several hours no urine was passed and in each individual there was a period of 9–12 h during which the excretion rate was relatively high, but the time at which this period started varied from 6 to 18 h; the net effect of this on the graph of average data is to indicate an extended period of moderately high urine flow rate not seen in any individual. A similar pattern for excretion of pethidine and norpethidine is seen also. The average data for the period after 39 h are based on only two cases and are therefore not very reliable.

The fluctuations in the rate of excretion of pethidine (figs 2 and 3) make it impossible to use the conventional method of kinetic analysis by fitting an exponential equation to the rate of excretion of drug against time. However, it was found that concentration
TABLE II. The amplitude and time constants of the exponential equation of pethidine concentration against time in each neonate and for the average data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Amplitude constant (nmol. ml(^{-1}))</th>
<th>Time constant (h)</th>
<th>No. of samples</th>
<th>F ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.1</td>
<td>32.3</td>
<td>6</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>42.6</td>
<td>10.0</td>
<td>5</td>
<td>60.9</td>
<td>0.004</td>
</tr>
<tr>
<td>3</td>
<td>24.2</td>
<td>14.9</td>
<td>5</td>
<td>32.3</td>
<td>0.01</td>
</tr>
<tr>
<td>4</td>
<td>23.4</td>
<td>14.1</td>
<td>7</td>
<td>8.8</td>
<td>0.03</td>
</tr>
<tr>
<td>5</td>
<td>5.7</td>
<td>45.4</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>79.3</td>
<td>16.1</td>
<td>8</td>
<td>150.2</td>
<td>0.00002</td>
</tr>
<tr>
<td>7</td>
<td>67.4</td>
<td>27.0</td>
<td>8</td>
<td>12.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean data</td>
<td>38.8</td>
<td>20.7</td>
<td>15</td>
<td>39.0</td>
<td>0.00003</td>
</tr>
</tbody>
</table>

Concentration (nmol. ml\(^{-1}\))

![Graph 4](image)

**Fig. 4.** Average urine concentration of pethidine and nortryptiline plotted against time. A single exponential curve for pethidine and a weighted cubic polynomial for norpethidine are shown.

![Graph 5](image)

**Fig. 5.** The amount (on a logarithmic scale) of pethidine that remains to be excreted by each neonate plotted against time.
PETHIDINE AND NORPETHIDINE IN THE NEWBORN

FIG. 6. The average amount (on a logarithmic scale) of pethidine that remains to be excreted plotted against time. Of pethidine in the urine declined fairly consistently with time. Therefore, a single exponential equation was fitted to the data for each individual; in five, the exponential was statistically significant (table II). In the others, pethidine concentration was almost constant (no. 5) or decreased rapidly only after 18 h (no. 1). An exponential derived from the mean data (fig. 3), obtained by dividing mean pethidine excretion rates by mean urine excretion rates and obtaining mean pethidine concentration against time, is highly significant \( (P = 0.00003) \), with a time constant of 20.7 h (fig. 4).

Norpethidine concentration did not decline exponentially with time. Polynomial equations (up to a cubic) were fitted to the fluctuations in norpethidine concentration but, in individuals, the scatter in the data was too great for any of them to be significant. However, for the average data (fig. 4) a cubic equation (taking account of sample frequency (Armitage, 1971)) gave a significant fit \( (P = 0.03) \). The fitted curve shows that norpethidine concentration decreased at first and then increased to a peak between 30 and 35 h before decreasing again.

Therefore, pethidine concentration in neonatal urine decays exponentially with time, whereas norpethidine concentration exhibits a decrease, an increase and then a further decrease.

The cumulative excretion of pethidine can be appreciated by plotting the total amount of pethidine remaining to be excreted by any time, against time. This was done for all individuals in figure 5 and for the average in figure 6. In figure 5, the initial slow decline (because of low urine flow) was followed by rapid excretion. The average data (fig. 6) showed a similar but smoother pattern with the excretion rate remaining almost constant after 12 h. An exponential equation fitted to the data from 12 h on was highly significant \( (P = 2 \times 10^{-9}) \) with a time constant of 10 h.

DISCUSSION

The results confirm that, following maternal administration of pethidine during labour, both pethidine and norpethidine are excreted in neonatal urine. Integration of the rates of excretion in figure 3 indicated that, in the first 24 h, the average neonate excreted 809 nmol of pethidine and 356 nmol of norpethidine. Expressing these figures as percentages of the maternal dose of pethidine facilitates a comparison with the results of other authors who administered varying doses of pethidine (table III). Way and colleagues (1949) reported a percentage excretion of pethidine similar to ours in similar circumstances although, in view of their assay method (table III), their figure for pethidine may include some norpethidine. Crawford and Rudofsky (1965) and O'Donoghue (1968, 1971) obtained greater percentage excretions after smaller doses, but in the work of Crawford and Rudofsky there were further differences of circumstance: i.v. injection, much shorter dose–delivery intervals and longer collection periods; also their assay method may not have reliably separated pethidine and norpethidine (Taylor, 1968).

Dose–delivery interval

O'Donoghue (1968) divided her data into three groups based on dose–delivery interval (table III). Although no statistical analysis is possible, since data for individuals were not given and the numbers in each group were small, it is apparent that, for both pethidine and norpethidine, the mean amounts...
excreted increased with dose–delivery interval. Regression analysis of Crawford and Rudofsky's (1965) data reveals a significant positive relationship between the amount of pethidine excreted \( y \) (nmol) and the dose–delivery interval \( t \) (h) for intervals of up to 0.55 h: \( y = 3134t + 27; P = 0.0009. \) In our study neonates, whose mothers were given pethidine 0.53 mmol (150 mg) i.m., excreted, during the first 24 h after delivery, amounts of pethidine and norpethidine which increased significantly with dose–delivery interval for intervals of up to 5 h: for pethidine, \( y = 438t - 384; P = 0.002; \) for norpethidine, \( y = 69t + 75; P = 0.04. \) Although it is surprising that other authors have not considered this aspect of their results, it seems quite clear that, after an injection of pethidine to the mother, uptake of pethidine by the foetus continues for at least 5 h.

This finding seems to conflict with the usual teaching (Bonica, 1967; Shnider, 1970; Crawford, 1972) that, following i.m. pethidine, peak depression in the newborn occurs if the baby is delivered between 1 and 4 h after administration and, conversely, that narcotic depression will be minimal if a baby is delivered before 1 h or more than 4–6 h after injection. This is based on assessments of short-term depression (such as the Apgar score at 1 min and the time to sustained ventilation). However, it is clear from our study that the total amount of pethidine transferred to the foetus increases with dose–delivery interval up to at least 5 h. Therefore, even if short-term depression is not detectable at this dose–delivery interval (5 h) more subtle but longer-term changes detected by neurobehavioural assessment (for example, Brackbill et al., 1974; Wiener, Hogg and Rosen, 1977a, b) may be more dependent on the total body content of pethidine and may, therefore, be affected even with dose–delivery intervals of 5 h or more. Accordingly, it should not be concluded that dose–delivery intervals greater than 4 h prevent all pharmacological effects in the neonate.

**Metabolism**

O'Donoghue (1968) administered pethidine 0.035 mmol (1 mg) to one neonate whose mother had received no medication during labour and, using thin-layer chromatography, found pethidine (780 nmol), and two metabolites, norpethidine (60 nmol) and pethidinic acid (220 nmol), in the urine collected over 24 h. Crawford and Rudofsky (1965), in a similar study in two neonates, collected urine for 48 h but found only pethidine (1050 nmol, 1580 nmol) in the urine, although the failure to detect metabolites may have been because of a lack of sensitivity and specificity of the methyl-orange method used (Taylor, 1968).

In the present study, average norpethidine concentration in urine showed a significant increase between 30 and 35 h (fig. 4). This suggests that, in addition to excreting norpethidine of maternal origin, the newborn is metabolizing pethidine to form norpethidine. This suggestion is supported by the following argument.

Since norpethidine is more polar than pethidine, its tubular reabsorption will be less and therefore its rate of excretion will almost certainly be greater than...
that of pethidine. Therefore, if the newborn were unable to produce norpethidine, that of maternal origin would be rapidly excreted and the ratio of norpethidine to pethidine would decrease with time. Yet in every neonate the ratio in fact increased, usually significantly \((0.1 > P > 0.0006)\). However, with one exception (no. 3) the slope of ratio against time was less than 0.08 h\(^{-1}\), whereas a similar analysis of Taylor’s (1968) data, for adults given pethidine 0.18 mmol (50 mg) i.v., gave a mean slope of 0.226 h\(^{-1}\), that is nearly three times as great as in our neonates. This argument confirms that the neonates can metabolize pethidine but the rate of \(n\)-demethylation to norpethidine is probably less than found in adults, as might be anticipated from less efficient neonatal hepatic function (Beckett, 1973).

**Excretion kinetics in adult and neonate**

For neonates in the present study, with normal uncontrolled urine pH, the rate of excretion of pethidine was markedly dependent on urine flow rate (figs 2 and 3) and did not decline exponentially. In Taylor’s (1968) study, in adults with controlled acid urine pH, the rate of pethidine excretion declined relatively smoothly and exponentially with time, even though urine flow rate varied over a range of approximately 5 : 1 in each individual. This suggests that the processes governing excretion in neonates may be different from those operating in Taylor’s adult study.

If the concentration of pethidine in urine (instead of pethidine excretion rate) is plotted against time, the distribution of Taylor’s observations in adults is broadly similar to that shown for our neonates in figure 4 and can be fitted by a single exponential. The importance of urine flow rate in the excretion process was then assessed as follows. For each measurement the ratio, of the measured concentration of pethidine \(C_m\) to the corresponding concentration read from the fitted exponential \(C_o\), was calculated. The linear regression of \(C_m/C_o\) on urine flow rate was then calculated.

In the adults (Taylor, 1968) the slope of the regression, of \(C_m/C_o\) on urine flow rate, was always negative and in two of the three subjects was significant \((P = 0.0025, 0.00002)\). In only three of the seven neonates was the slope negative and in only one of these was it significant \((P = 0.004)\). In the other six, \(P\) ranged from 0.1 to 0.75. Therefore, in general for neonates, an increase in urine flow rate produced no change in urine pethidine concentration but did produce an increase in the rate of pethidine excretion. Conversely for adults, an increase in urine flow rate produced a decrease in urine pethidine concentration but no change in the rate of pethidine excretion. A possible explanation of these differences is as follows.

For the adults, increases in urine flow rate were probably a result of fluid intake producing a reduction in the amount of plasma water reabsorbed in the renal tubules, with little or no change in glomerular filtration rate (GFR). Therefore the rate of excretion of pethidine from plasma to glomerular filtrate \((\text{GFR} \times \text{free-pethidine plasma concentration})\) would remain essentially constant. Furthermore, under conditions of acid urine pH, almost all the pethidine in the urine would be ionized and unavailable for reabsorption. Therefore, if the rate of reabsorption of water at the tubules decreases, urine flow increases and pethidine concentration in the urine decreases but the rate of excretion of pethidine changes little.

In our neonates, at least part of the increase in urine flow rate may be attributed to an increase in glomerular filtration rate following an increase in renal blood flow (Oh, Oh and Lind, 1966). Therefore, if there is no change in the fraction of water reabsorbed, an increase in urine flow rate would produce no change in urine pethidine concentration, but would produce an increase in the rate of excretion. Even if the fraction of water reabsorbed increases following an increase in glomerular filtration rate, or following feeding as in adults, there would still be little change in urine pethidine concentration because, with the urine pH found under normal conditions, less of the pethidine would be ionized and more would be available for reabsorption.

**Time for elimination of pethidine**

In adults, plasma concentrations in normal volunteers decline according to two exponentials, the slower of which has a time constant of about 5 h (Klotz et al., 1974; Mather et al., 1975; Stambaugh et al., 1976); accordingly elimination would be 95% complete in less than 15 h.

In the neonate, the time for elimination of pethidine can be estimated from the present data in two ways. Using the plot of concentration in urine against time for the average data (fig. 4) an exponential curve with a time constant of 20.7 h was obtained. On this basis, assuming body burden to be approximately proportional to concentration in urine, 95% of the drug would be eliminated in approximately 62 h (three time constants). An alternative method (fig. 6) provides an exponential with a time constant of only 10 h. However, this latter time constant applies only during
the period of high urine excretion rate. In the first 12 h there is little excretion (fig. 6) and, after the period of high urine excretion, the pethidine excretion rate can be expected to decrease, as can be seen in some individuals in figure 5. Therefore, a lower limit to the time for 95% elimination of the pethidine would be set by 12 h plus three 10-h time constants, that is 42 h. Therefore, by the 3rd day (between 42 and 62 h) there should be little pethidine remaining in the body to exert any pharmacological effect. It seems unlikely, therefore, that effects seen in neonates much beyond the 3rd day of life (Richards and Bernal, 1972) could be a result of a direct pharmacological action of pethidine or its metabolites and some other explanation may be necessary. On the other hand, it has been demonstrated that the effects of pethidine on ventilation and feeding are apparent for up to 48 h after birth (Wiener, Hogg and Rosen, 1977a, b). Therefore, if it is considered desirable to reverse these effects of pethidine in the newborn by the administration of a narcotic antagonist, it may be necessary to continue the administration for up to 3 days.

ACKNOWLEDGEMENTS

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REFERENCES


EXCRETION URINAIRE ET METABOLISME DE LA PETHIDINE ET DE LA NORPETHIDINE CHEZ LE NOUVEAU-NE

RESUME

On a recueilli pendant les premières 24–40 h de leur vie, l’urine de sept nouveau-nés, dont les mères avaient reçu de la pethidine pendant le travail. On a mesuré le volume urinaire et le pH, de même que les concentrations de pethidine et de norpethidine dans l’urine. Le débit d’urine a été faible pendant les 7 à 22 premières heures, puis élevé pendant environ 12 h. Le taux d’excrétion de la pethidine et de la norpethidine a été à peu près parallèle au débit d’urine. Cependant, le taux d’excrétion de la norpethidine par rapport à celui de la pethidine a augmenté avec le temps alors que la concentration de norpethidine dans l’urine a d’abord diminué, puis, après 18 h, augmenté d’une manière significative. Ces observations impliquent que le nouveau-ne peut métaboliser la pethidine, bien que son taux de métabolisme soit probablement plus faible que celui de l’adulte. Les quantités totales de pethidine et de norpethidine excrétées pendant les 24 premières heures qui ont
suivi la naissance ont été positivement reliées à l'intervalle “administration de la dose/accouchement” de la mère pour des intervalles allant jusqu'à au moins 5 h. A partir des données, on a estimé que 95% du total de la pethidine transférée par la mère sont éliminés par le bébé dans les 2 ou 3 jours qui suivent la naissance.

EXCRECION DE ORINA Y METABOLISMO DE PETIDINA Y NORPETIDINA EN EL RECIEN NACIDO

SUMARIO

En siete neonatos, cuyas madres recibieron petidina durante el parto, se recolectó orina durante las primeras 24 a 40 horas de vida. Se midieron el volumen de orina y pH y concentraciones de petidina y norpetidina en la orina. La cantidad de orina resultó baja en las primeras 7 a 22 h, luego alta durante aproximadamente 12 h. La cantidad de excreción de petidina y norpetidina fue aproximadamente paralela a la de orina. Sin embargo, la relación de la cantidad de excreción de norpetidina comparada con la de petidina aumentó con el paso del tiempo y la concentración de norpetidina en la orina disminuyó primero y luego, al cabo de 18 h, aumentó en forma significativa. Estos datos indican que el neonato puede metabolizar petidina, aunque el grado de metabolismo probablemente sea menor que en el adulto. Las cantidades totales de excreción de petidina y norpetidina en las primeras 24 h siguiendo el parto estaban directamente relacionadas al intervalo entre dosis y parto en la madre en intervalos de hasta por lo menos 5 h. De los datos obtenidos se estima que un 95% del total de petidina transferida de la madre sería eliminado por el bebé al segundo o tercero día de nacido.