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ADMINISTRATION AND COMPOUNDING OF EUTHANASIC AGENTS

Royal Dutch Society for the Advancement of Pharmacy
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1. Introduction

After many years of a political discussion about euthanasia and assisted suicide, a system has been chosen in which criminal liability is in principle maintained and physicians must plead force majeure as mentioned in Article 40 of the Penal Code. This makes it possible to treat all forms of life-ending treatment in the same way procedurally. The manner in which the physician must report in writing to the municipal coroner is now established in the Order forming part of the Law on Disposal of the Dead which went into force on June 1, 1994. Among the many points to which the reporting physician must pay attention pursuant to this Order is the matter of *in what way* and *by what means* the ending of life is effected [Med Contact 1994; 49:697-9].

The Board of Governors of the KNMP, the Royal Dutch Society for the Advancement of Pharmacy, long ago recognized that physicians and pharmacists must have reliable data on the technical practice of euthanasia. In 1985 it assigned a Task Force to report "on the information currently available concerning the requirements that substances must meet in order to be administered as euthanasic agents and substances which currently meet these requirements and the extent to which they do so." This Task Force issued its "Technical Report on Euthanasic Agents" in 1987. In that report the Task Force made an inventory of and evaluated the published and unpublished experiences with euthanasic agents of which it had knowledge at the time and, based on that, developed concrete recommendations in the matter of various modes of administration of euthanasic agents.

The present brochure replaces the original Report of 1987. Since at that time the Task Force had to base itself, in part, on theoretical considerations and/or experience with agents that were not or were seldom administered as euthanasic agents, feedback from practice concerning the applicability of the Task Force's recommendations was deemed necessary. To this end, each copy of the Report was accompanied by a questionnaire, with the request to copy it, fill it in, and return it anonymously. In 1994 the Task Force reviewed the survey forms received and adjusted its initial recommendations on the basis of that evaluation. The KNMP's Board of Governors decided to issue the new recommendations, furnished with an extensive explanation, as a brochure again. Since the Board still regards such information as sensitive, it has decided not to make this new report, like the previous one, public, but to make it available exclusively to individual physicians and pharmacists who request it in writing.

This new brochure is laid out as follows. After a short introduction (*Chapter 1*), a recapitulation of the recommendations of 1987 and of the considerations on which they were based is presented (*Chapter 2*). In *Chapter 3* there is an extensive discussion of the results that the Task Force found in its survey and the conclusions derived from them. *Chapter 4* explains how the Task Force's original recommendations were modified. Since only some of these recommendations can be carried out with mass-produced products, specific dispensing directions follow in *Chapter 5* . Lastly, *Chapter 6* describes the criteria for diligence which the pharmacist must keep in mind when supplying euthanasic agents.

2. Old Recommendations

2.1. Inventory Taken in 1987

In 1987 the KNMP's Euthanasics Task Force reported the following inventory and evaluation of euthanasic agents:

Barbiturates

A sufficiently large dose of a barbiturate will cause respiratory acidosis via depression of the respiratory centers. This, together with vascular and/or heart shock, will lead to death. For oral administration, preference is given to a lipophil barbiturate (pentobarbital, secobarbital), which passes the blood-brain barrier relatively quickly and thus acts rapidly. Because death sometimes may not occur for two to five days, the Task Force gives preference to a combination with another euthanasic agent. In the past central nervous system depressants such as diazepam or alcohol were recommended, but the simultaneous use of dextropropoxyphene and/or orphenadrine appears to be more practical (see below). Of course, it is also possible, when the comatose state has been obtained, to inject a neuromuscular muscle relaxant if desired.

For intravenous administration, thiopental receives most consideration. It is not possible to administer so much of it that a lethal effect is guaranteed, but the substance is quite suitable for producing coma, after which termination may be effected using a muscle relaxant (see below).

Rectal administration is not favored. A clyster, because of the position that the patient must assume (and maintain) for it, is not practical. In the case of suppositories, availability is greatly dependent upon the patient's ability to retain them. Suppositories may act as laxatives and also entail the risk that the active ingredient is only slowly released. In addition, the lethal quantity of barbiturate cannot be incorporated into a single suppository, so that several are required. When administered all at one time absorption is unpredictable and, because of the large quantity of substance, there may be severe irritation. Repeated administration has the psychological drawback that administration must be effected in a patient who has already become comatose.

Benzodiazepine derivatives

Since it is very difficult to induce a coma by oral administration of a benzodiazepine derivative, intravenous administration was advised. Nevertheless, cases are known in which even 40 mg of diazepam given intravenously appeared to be insufficient. Flunitrazepam and midazolam perhaps have a more reliable action, but there is as yet insufficient experience with these, so that thiopental receives preference. (see above).

Neuromuscular muscle relaxants

An adequate quantity of a neuromuscular muscle relaxant administered intravenously produces complete paralysis of all striated muscles within a few minutes. This results in asphyxia and death due to anoxemia. A disadvantage may be that some patients become cyanotic. Naturally, these substances may be administered only in a comatose patient. If there is the slightest doubt about this, a coma must first be induced by intravenous administration of thiopental (see above).

No consideration is given to the depolarizing agent suxamethonium, since this substance, even in very high dosage, acts for too brief a period of time to be useful as a euthanasic agent. Non-depolarizing agents (such as alcuronium and pancuronium) are most appropriate. These may best be given by intravenous administration. If this is not possible, intramuscular administration seems to be an acceptable alternative. Theoretically speaking, here the risk exists that release of the substance from the muscle is irregular and hence not so reliable. Experience with intramuscular injection as a euthanasic, however, suggests that an adequate effect can be obtained within a limited time, provided that a high dose is injected in the proper way. Oral or rectal administration does not enter into consideration because, due to

their quaternary structure, muscle relaxants are poorly absorbed by these routes of administration.

Opiates

When a patient has not previously been treated with an opiate, intravenous administration of an adequate dose can rapidly lead to asphyxia and to death due to anoxemia, via severe depression of the respiratory centers and a period of Cheyne-Stokes respiration. However, administration as an intravenous infusion liquid in slowly increasing dosage must be avoided, in view of the possible rapid appearance of tolerance.

Terminal patients who have already been on an opiate for a lengthy period of time are tolerant to the respiratory depressive effect. Having such patients fall asleep for good with the aid of an opiate is often unsuccessful, even when a high dose is used. Another special problem may be that some opiates (such as buprenorphine and pentazocine) have antagonistic as well as agonistic properties. Their administration may sometimes produce acute withdrawal symptoms and thus is not recommended.

In view of reports of fatal poisoning with dextropopoxyphene, the Task Force sees a possibility in the addition of this agent to an oral barbiturate. It expects that this combination makes it more certain that death will occur within a foreseeable time (in 1-5 hours). Whether the action of dextropropoxyphene is based on respiratory depression alone or also involves circulatory shock remains to be seen. The general disadvantage of opiates, that long-term use prior to euthanasia may lead to great tolerance, however, also applies to dextropropoxyphene. At least one case is known in which the patient had become so tolerant that 2.25 g of dextropropoxyphene hydrochloride had an insufficient result.

There are no indications that an oral barbiturate could better be combined with another opiate. Bezitramide does not seem to be an appropriate choice, since vomiting may occur even at low doses. In addition, absorption is slow and irregular.

Orphenadrine

Cases of poisoning with orphenadrine often seem to take a lethal course. Fatal asphyxia may appear as soon as 2-3 hours after ingestion. If the patient is [not] treated for this in good time, cardiotoxic effects may become manifest, which may be fatal 12-18 hours after ingestion. On the basis of these observations, the Task Force sees a possibility in the combination of an oral barbiturate with orphenadrine. However, no experience has been had with this.

Ketamine

At first glance, ketamine seems to be suitable for producing a coma by intramuscular administration. However, disadvantages are that too great a volume must be injected, that the patient seems to be more alert during ketamine-induced narcosis and that convulsions may occur.

Insulin

Parenteral administration of insulin in sufficiently high dosage produces a hypoglycemic coma that leads to death. How rapidly this will take place depends upon the patient's condition. Death takes at least hours and sometimes days to occur. The depth of the coma may vary and even decrease in the course of time, as a result of which a supplementary dose must be administered. During a superficial coma the patient may be quite restless and have convulsions.

Other agents

A large dose of cardiac glycoside or a beta-blocker can lead to death via heart or cardiovascular shock. Cardiac arrest can also be produced by giving a high dose of potassium chloride intravenously. Naturally, these agents cannot be given while the patient is still conscious. Their administration is not very customary. When given in great

overdosage, lidocaine can cause respiratory insufficiency and cardiac arrest. But convulsions are also seen, so that this agent is not suitable for euthanasia. Cholinesterase inhibitors inhibit vomiting of acetylcholine, with resultant stimulation of muscarine and nicotine receptors. Symptoms of poisoning include respiratory arrest, bradycardia and ECG alterations, among others. Convulsions also appear with compounds acting on the central nervous system, in contrast to substances with a quaternary ammonium group. So far as is known, no experience has been had with their administration as euthanasics.

Associated with some of these other agents is the practical disadvantage that they may also be obtained outside the pharmacy.

2.2. Recommendations in 1987

On the basis of the considerations in Chapter 2, in 1987 the KNMP's Euthanasics Task Force developed the following recommendations in the matter of administration of euthanasic agents:

Oral Administration

To reduce the chances of the euthanasic being thrown up, an antiemetic must first be given for a day.

Actual euthanasia can best be effected by ingestion of the contents of 20 capsules Depronal (equivalent to 3 g *dextropropoxyphene hydrochloride*) after mixture with a little custard, pudding or yogurt. This must immediately be followed by administration of 100 ml of a potion with 9 g *secobarbitral sodium* (or *pentobarbital sodium*). When dealing with a patient who is or may be tolerant to dextropropoxyphene, not a barbiturate potion, but 100 ml of a potion with 9 [g] barbiturate and 3 g *orphenadrine hydrochloride* must be used in addition to dextropropoxyphene. Since vomiting is experienced with the administration of orphenadrine as a euthanasic, addition of this substance to dextropropoxyphene plus barbiturate is preferable to the combination of orphenadrine plus barbiturate without dextropropoxyphene.

Parenteral administration

First a coma is induced by intravenous administration of 1 g *thiopental sodium* (Nesdonal), if necessary, 1.5-2 g of the product in case of strong tolerance to barbiturates. Then 45 mg *alcuronium dichloride* (Alloferin) or 18 mg *pancuronium dibromide* (Pavulon) is injected. In order to ensure optimal availability, these agents are preferably given intravenously. However, there are substantial indications that they can also be injected intramuscularly. In severe hepatitis or cirrhosis of the liver alcuronium is the agent of first choice.

Rectal administration

Euthanasia by the rectal route has such disadvantages that this method may at most be considered if other modes of administration seem to be unfeasible. When this is the case, a suppository containing 1 g *pentobarbital sodium* or *secobarbital sodium* in a fatty base may be considered, the possible dosage being three suppositories every hour. Here it is of great importance to check that the patient's body temperature is not or does not go so low that the suppositories fail to melt thoroughly. The physician must be fully prepared, if necessary, to terminate with a parenteral muscle relaxant when death has not taken place after the administration of 15 suppositories.

3. Evaluation of Old Recommendations

In its first report, the KNMP's Euthanasics Task Force noted that there were hardly any reliable data in the literature concerning euthanasic agents and that in its recommendations it could depend only partly on practical experience. For another thing, it had to base itself on theoretical considerations and/or experience with agents which were not or were seldom used as euthanasics. Thus the Task Force then deemed it necessary to receive feedback from practice concerning the applicability of its recommendations, so that these could be

tested and adjusted. To this end, each copy of the report was accompanied by a questionnaire with the request to copy it, fill it in and return it anonymously. Since this anonymity meant that no further information could be obtained, detailed inquiry into the following particulars was made in the form:

- *Patient data:* sex and age; presence of liver or kidney dysfunction; ailment and physical condition; medication history.
- *Agents administered:* premedication, if any; actual euthanasic agents; whether or not combined with alcohol.
- *Presence of physician:* during/after administration.
- *Course:* vomiting or other problems in administration; times at which coma and death occurred; death due to cardiac arrest or respiratory arrest; complications, if any; additional regulations.
- *General remarks:* e.g., suggestions for improving the recommendations.

In the years 1987-1993, 165 completed forms suitable for evaluation were returned to the KNMP's Task Force. In this period, 980 reports were furnished to 980 physicians and 940 to pharmacists. The Task Force assessed the forms in early 1994. At that moment the Task Force consisted of the following members: Dr. P.V. Admiraal; Drs. J.A.L. van Lakwijk-Najoan, Chairman; Drs. A.C. van Loenen; Drs. G.B. Schmidt; Drs. S.M. Dreijer-van de Glas; Dr. P.A.G.M. de Smet, Secretary.

3.1 Results

Patient data

The 165 returns concerned 69 females (41.8%) with an average age of 65.9 years and 92 males (55.8%) with an average age of 64.9 years. In 4 patients (varying in age from 70 to 89 years), the sex was omitted (2.4%). In 132 cases (80%), a malignant process was involved. No noteworthy associations between specific patient characteristics and the course of euthanasia were reported.

Oral administration

A detailed specification of the agents administered, dosages and course in the 87 cases of oral euthanasia is given in Table 1. In one case, an 85-year-old female died 5 hours after taking a potion containing 200 mg morphine. In the other 86 cases use was made of a barbiturate in combination with, or without, dextropropoxyphene and/or orphenadrine. In accordance with the Task Force's recommendations, an antiemetic was administered beforehand in 59 cases, metoclopramide having been the main choice (n = 44). Several previously treated patients were very queasy but did not vomit. This in contrast to 2 patients (an 81-year old female with leukemia and a female of 57 with carcinoma of the colon) who had taken no antiemetic and vomited their euthanasic agents.

Table 1. Agents administered, doses and course in 87 cases of oral euthanasiaa

Agent(s) administered + dose(s)	No. cases	Time from ingestion to death (in minutes or hours)
Barbiturates (n = 28)		
Secobarbital 3 g	1	5'
Pentobarbital 4.5 g	3	2x20' and 1x2h10'
Phenobarbital 6 g	1	Ended by means of 100 mg morphine I.V. after 5h30'
Amobarbital 8 g	1	Ended by means of muscle relaxant after 15'
Seco-/pentobarbital 9 g	20	4x15' 4x20' 1x25' 2x30' 1x70' 3x4h and 1x7h 4x ended by means of muscle relaxant (after 30' 60' 4h and 6 h)
Phenobarbital 10 g	1	60'
Voxparax( ) 36 tab.b	1	15'

Dextropropoxyphene + barbiturate (a = 29)

Dextropropoxyphene 3 g + pentobarbital 4.5 g 1 45'
Dextropropoxyphene 3 g + seco/pentobarbital 9 g 28 1x2' 1x8' 2x10' 6x15' 2x20' 1x25' 2x30' 1x35' 2x45' 2x60' 1x95' and 2x2h
4x ended by means of muscle relaxant (after 40' 2h20' 5h30' and 24h)
1x most vomited

Orphenadrine + barbiturate (n = 13)

Orphenadrine 1.5 g + pentobarbital 4.5 g 1 Ended by means of muscle relaxant after 2 h
Orphenadrine 3 g + seco-/pentobarbital 9 g 11 1x15' 1x20' 1x25' 1x30' 1x45' and 1x60'
5x ended by means of muscle relaxant (after 5'c 70' 90' 12 h and 13 h)
Orphenadrine ? g + pentobarbital ? g 1 Most vomited

Dextropropoxyphene + orphenadrine +

barbiturate (n = 16)

Dextropropoxyphene 3 g + orphenadrine 3 g +
seco-/pentobarbital 9 g 16 1x5' 1x15' 3x20' 2x35' 1x60' 2x90' 1x2h 1x6h and 1x 24h
2x ended by means of muscle relaxant after 60' and 5h30'
1x most vomited

Other (n = 1)

Morphine 0.2 g 1 5h

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a Salt designations have been omitted for the sake of clarity. Substances and doses recommended by the KNMP's Euthanasics Task Force are italicized

b Composition per tablet: 50 mg hydroxyzine HCl, 50 mg brallobarbital Ca and 150 mg secobarbital Na

c In connection with persistent choking due to retrocession of the tongue upon immediate fall into coma In most cases the dosage recommendations of the KNMP's Euthanasics Task Force, namely 9 g secobarbital sodium or pentobarbital sodium, 3 g dextropropoxyphene hydrochloride and/or 3 g orphenadrine hydrochloride, were followed (n = 75). However, the Task Force's recommendation to combine the barbiturate with dextropropoxyphene, with or without supplementation by orphenadrine, in order to increase the likelihood of a rapid death, was regularly ignored here. As appears in Table 2, the results of these alternative methods were comparable with those of the Task Force's recommendations. In 58 of the 75 cases (77%) the patient died without further intervention and in only 3 cases (4%) did death take place after more than 5 hours. In 15 cases (20%) termination was effected with a muscle relaxant. Given as reasons were, among others, that when the potion was taken slowly the patient was sometimes already asleep before the entire quantity had been ingested. In 2 patients breathing became so inhibited when coma set in that the physician administered a muscle relaxant for that reason. In 6 cases the muscle relaxant was given after more than 5 hours, so that the total number of patients who remained alive longer than 5 hours comes to 9 patients (12%).

A distinctly unpleasant effect of the potions is their bitter taste; this was commented on 12 times, unasked.

Table 2. Course in 75 cases of oral euthanasia following KNMP's Euthanasics Task Force

dosage recommendations

Agent	Vomiting	0-1h	1-5h	term. > 5ha	Total 0-5h
Barbiturate	-	11 (55%)	4 (20%)	3 (15%)	wo: 1 (5%) w: 1 (5%) 20 (100%)
Dextropropoxy. + barbiturate	1 (4%)	20 (71%)	3 (11%)	2 (7%)	wo: - (0%) w: 2 (7%) 28 (100%)
Orphenadrine + barbiturate	-	6 (55%)	- (0%)	3 (27%)	wo: - (0%) w: 2 (18%) 11 (100%)
Dextropropoxy. + orphenadrine + barbiturate	1 (6%)	8 (50%)	3 (19%)	1 (6%)	wo: 2 (13%) w: 1 (6%) 16 (100%)
Total	2 (3%)	45 (60%)	10 (13%)	9 (12%)	wo: 3 (4%) w: 6 (8%) 75 (100%)

a wo = without further intervention; w = with further intervention

Parenteral administration

Detailed data on 73 parenteral cases of euthanasia are shown in Table 3. In 17 cases (23.3%) the Task Force's recommendations to first induce a coma with thiopental and then terminate with a muscle relaxant were not followed. In 14 cases not thiopental, but a benzodiazepine (diazepam, midazolam) or an opiate (morphine, nicomorphine), was used to start, while in 3 cases morphine or potassium chloride was given instead of a muscle relaxant. In one case coma did not set in until after the third dose of diazepam (40 + 20 + 50 mg I.V.), while in another case after the administration of alcuronium a patient previously treated with midazolam "opened his eyes and beckoned to his family" before dying. Also reported was a case in which a 54-year old male received morphine infusions for two weeks, in doses ranging from 20 mg/24 hours to 100 mg/hour. On the day of euthanasia this patient received another 600 mg I.V., after which he was subcomatose for only 20 minutes and then reawoke. After 24 hrs he was terminated by means of thiopental and potassium chloride.

In 56 cases (76.7%) the recommended combination of thiopental I.V. with a muscle relaxant was chosen. In 11 of these cases (19.6%) the patient died immediately after the administration of thiopental, even before the planned muscle relaxant could be given. In the remaining 45 cases (80.4%) the administration of thiopental was followed by a muscle relaxant (alcuronium or pancuronium):

- In 39 cases both agents were given intravenously without any further addition and the patient died as the result of anoxemia caused by the muscle relaxant. Respiratory arrest occurred within a few minutes, but complete cardiac arrest sometimes took 15 min.
- In 2 cases, in addition to thiopental and alcuronium, intravenous potassium chloride was also given to hasten cardiac arrest.
- In 2 cases, although intravenous injection was intended, administration was probably extravasal and death was delayed.
- In 2 cases the muscle relaxant was given not intravenously but intramuscularly, and death occurred only after 30-75 min.

Table 3. Agents and doses administered in 73 cases of parenteral euthanasiaa

Agent(s) and dose(s) administered	Number of cases

Thiopental I.V. (n = 11)b

Thiopental 1 g 8
Thiopental 1.5 g 2
Thiopental 2 g 1

Thiopental I.V. + muscle relaxant I.V./I.M./I.A. (n = 45)

Thiopental 0.5-2 g I.V.c followed by pancuronium 8 mg I.V. 2
pancuronium 10 mg I.V. 2
pancuronium 12 mg I.V. 1
pancuronium 20 mg I.V. 3
pancuronium ? mg I.V. 2
alcuronium 30 mg I.V. 6
alcuronium 45 mg I.V. 5
alcuronium 50 mg I.V. 16
alcuronium ? mg I.V. 2
Thiopental 1 g I.V. followed by alcuronium 50 mg I.V. 1d
Thiopental 1 g I.V. + alcuronium 30 mg I.V. followed by 1 g thio-
pental I.V. + 20 mg alcuronium I.V. 1e
Thiopental 1 g I.V. followed by alcuronium 45 mg I.V. + KCl 2 g I.V. 1
alcuronium 50 mg I.V. + KCl 2 g I.V. 1
Thiopental 1 g I.V. followed by pancuronium 30 mg I.M. 1f
alcuronium 30 mg + 20 mg I.M. 1g

Other central nervous system depressants + muscle relaxant

I.V./I.M. (n = 14)

Diazepam 10 mg I.V. followed by alcuronium 30 mg I.V. 1
Diazepam 10 mg I.V. followed by alcuronium 40 mg I.V. 1
Diazepam 30 mg I.V. followed by pancuronium 12 mg I.V. 1
Diazepam 40 mg I.V. followed by pancuronium 18 mg I.V. 1
Diazepam 40 mg I.V. followed by pancuronium 32 mg I.V. 1
Diazepam 50 mg I.V. followed by alcuronium 50 mg I.V. 1
Diazepam 50 mg I.V. followed by alcuronium 20 mg I.V. 1
Diazepam 50 mg I.M. + 1 g thiopental I.M. followed by
50 mg alcuronium intra-arterially 1h
Diazepam 40 + 20 + 50 mg I.V. followed by alcuronium 30 mg I.V. 1i
Nicomorphine 50 mg I.V. + 50 mg I.V. followed by alcuronium 50 mg I.M. 1
Morphine 120 mg I.M. followed by alcuronium 45 mg I.M. 1
Morphine 100 mg I.V. followed by alcuronium 45 mg I.V. 1
Morphine ? mg I.V. followed by pancuronium 20 mg I.V. 1
Midazolam 45 mg I.M. followed by alcuronium 50 mg I.V. 1j

Other agents I.V./I.M. (n = 3)

Morphine infusions for 2 weeks followed by thiopental 0.5 g I.V.
followed by KCl 50 mg I.V. 1k
Diazepam 50 mg I.M. followed by morphine 60 mg I.V. 1l

Morphine 1x20 mg + 3x60 mg I.M. followed by thiopental 2 g I.V. + morphine 100 mg I.V. 1m	

a Salt designations have been omitted for the sake of clarity.
b These 11 patients died before a muscle relaxant could be administered.
c The dose of thiopental was 2x 0.5 g, 29x 1 g, 1x 1.5 g and 4x 2 g; in 3 cases the dose was not reported.
d In 1 case 1 g thiopental and 50 mg alcuronium were administered I.V., but probably were injected partly extravasally, since the patient only died after 45 min.
e First dose of thiopental was injected extravasally and 30 mg alcuronium also had no effect. After 1 hour 1 g thiopental and 20 mg alcuronium were again administered I.V. Since the patient only died after 75 min., it may be assumed that only part of the second intravasal dose reached its destination.
f Patient died after 30 min.
g Because of doubt of the effect of 30 mg alcuronium I.M. in the thigh, another 20 mg alcuronium was administered I.M. in the upper arm. The patient died 75 min. after the administration of thiopental.
h Patient fell into a coma 25 min. after the administration of thiopental and died after the administration of alcuronium.
i Repeated administration of diazepam was necessary to induce a coma.
j After the administration of alcuronium "the patient opened his eyes and beckoned to his family" before dying.
k Morphine infusions were increased from 20 mg/24 hours to 100 mg/hour. On the day of euthanasia another 600 mg I.V. were administered, which led only to a subcoma lasting 20 min. After 24 hours life was ended with thiopental and potassium chloride.
l Patient died 60 min. after the administration of morphine.
m Patient died immediately after the last administration of morphine.

Rectal administration

A detailed listing of the 5 cases of rectal euthanasia is presented in Table 4. In 2 cases the patient died within 3 hours without further intervention, while in the other cases termination was effected with a muscle relaxant after 30 min. to 5 hours.

Table 4. Agents and doses administered, and course in 5 cases of rectal euthanasiaa

Agent administered	Dose	Dosage interval	Time from insertion to death (in minutes or hours)
Pentobarbital supp.	1 g	2x	3 supp. 1h 70'
Secobarbital supp.	0.5 g	3x	2 supp. 1h Ended by means of muscle relaxant after 2h
Secobarbital supp.	1 g	1x	3 supp. - Ended by means of muscle relaxant after 30'
Ditto	3x	3 supp. 1h	2h30'
Supp. containing			
200 mg hydroxyzine	7x	1 supp. 30'	Ended by means of muscle relaxant after 5h
450 mg secobarbital			
150 mg amobarbital			
200 mg heptobarbital			
200 mg cyclobarbital			

a Salt designations have been omitted for the sake of clarity.

Presence of physician

In most cases the physician was present during and after administration of the euthanasic agent. This of course was the case for all patients in whom euthanasia was effected by the parenteral route. In non-parenteral cases the physician did not always stay to await the moment of death. In some cases the physician returned to end the coma with the aid of a

muscle relaxant.

3.2. Discussion

It is quite natural to compare the results described above with those of other Dutch researchers, in particular with the findings of:

- Maas PJ van der, Delden JJM van, Pijnenborg L. "Medische beslissingen rond het levenseinde" [Medical decisions on the end of life]. The Hague: SDU, 1991
- Wal G van der. "Euthanasie en hulp bij zelfdoding door huisartsen" [Euthanasia and assisted suicide by general practitioners]. Thesis. Rotterdam: WYT Uitgeefgroep, 1992.

However, a direct comparison seems difficult. Since the questionnaire was enclosed whenever a copy of the report of the KNMP's Euthanasics Task Force was requested, all respondents may be expected to have been familiar with the contents of the said report and with the recommendations given in it. However, this does not necessarily apply to the physicians who were surveyed by van der Maas and coworkers or van der Wal. Thus, it is not surprising that these authors found a sizable number of drugs which were administered in a variety of combinations and in different ways, so that a breakdown such as has been made here is not so simple. Van der Wal assumes that, when it came to actual choice of the euthanasic agent, easy availability may have played a role for the practitioner. This carried the risk of an unsuitable method leading to disappointment.

In the great majority of cases evaluated by us (160/165 = 97%), oral or parenteral administration was adopted. Undoubtedly a factor in the choice between these two modes of administration is the consideration that when muscle relaxants are administered the patient dies directly after administration, so that there is a clear and immediate association between cause and effect. This may be psychologically difficult for the individual physician, certainly when euthanasia is practiced for the first time. Another serious consideration may be that intravenous administration does not always seem to be easy. In the group of physicians who appear to have given a barbiturate potion there are surely some who believe that when a patient wishes euthanasia, he must carry it out himself. However, then the physician must be willing to be present and end the coma when necessary.

A clear general conclusion may be drawn as concerns the lethal action of the euthanasic agents recommended by the KNMP's Task Force: the administration of thiopental followed by a muscle relaxant - provided the latter is properly administered - causes immediate death without any problems and may therefore be safely recommended.

Oral euthanasia

In more than half the cases reported (86/165 or 52%), a barbiturate was selected, alone or in combination with orphenadrine and/or dextropropoxyphene. Here the dosage recommendations of the KNMP's Euthanasics Task Force were usually followed. These appeared to be quite satisfactory in practice: 73% of the patients died in the first 5 hours after administration and in 60% death occurred within the very first hour. In individual cases , however, death was longer than 5 hours in coming and in one case the patient was still alive after 24 hours. Strikingly enough, it does not appear from the survey that addition of orphenadrine and/or dextropropoxyphene to the barbiturate increases the likelihood of death taking place within a measurable time, as the Task Force initially supposed. On the contrary, even with these combinations individual cases may take longer than 5 hours and it may sometimes appear necessary to terminate with a muscle relaxant 24 hours after administration as well. Since the comparability of the various patient groups was not established and the numbers of patients in each group are not very large, it cannot be concluded from this that administration of a barbiturate alone has the same effect as a combination. Nevertheless, in the practical experience that has become available the Task Force sees insufficient cause for maintaining its original, merely theoretical, preference for combinations. For this reason, the Task Force now recommends carrying out oral euthanasia with a barbiturate potion without the addition of orphenadrine and/or dextropropoxyphene.

The results of the survey present no reference point for modifying the original dosage recommendation of 9 g barbiturate. Thus this recommendation is retained, partly because

research by van der Maas and coworkers and van de Wal indicates that euthanasia may proceed more slowly when lower doses are used. Since 9 g barbiturate would not always appear to lead to rapid death, the physician must be prepared, if necessary, to inject a muscle relaxant when death is delayed (e.g., takes longer than 5 hours). Terminating with a muscle relaxant may also be advisable when, for example, the patient falls asleep before having ingested the whole potion and/or such severe distress is produced upon onset of coma that bystanders get the impression that the patient is suffocating.

The results of the survey show that pretreatment with an antiemetic, such as metoclopramide, is advisable. This recommendation is thus also retained. In the light of the many comments concerning the unpleasant taste of barbiturate potions, their composition was adjusted (see *Chapter 5*). Although this improves the taste somewhat, they will still be found to be unpleasant, mainly because of their high pH. It is advisable to warn the patient of this.

Parenteral euthanasia

It appears from the results that intravenous administration of thiopental followed by a muscle relaxant (45/165 or 27%) is the most reliable route for producing euthanasia. In contrast to oral euthanasia, this mode of procedure is independent of factors which affect the extent and speed of gastrointestinal absorption. In elderly cachectic terminal patients, however, intravenous injection may not always be easy to accomplish. For this reason, it is recommended that a needle first be attached to a plastic cannula equipped with a Y-type attachment, thus guaranteeing the administration of two agents successively. The place most indicated is the dorsum of the hand; in addition, a good thrust and good "floodlighting" are essential. Although intramuscular administration of muscle relaxants (after *intravenous* administration of thiopental) may be considered as an alternative, it must be kept in mind that the time lapse becomes longer. Here too, a sober consideration of administration should be made in advance; only an injection into a well irrigated, nonedematous muscle which is followed by massage gives the best results.

The matter of availability of parenteral euthanasics involves the problem that the recommended muscle relaxants and thiopental are supplied by the wholesale trade only in comparatively large numbers. The Task Force offers the suggestion that such large packagings be ordered regionally and the agents then supplied in smaller numbers. Since in most cases 1 - 1.5 g thiopental sodium seems to be effective and this quantity can conveniently be dissolved in a small volume (10 ml physiological saline), the Task Force henceforth recommends an intravenous dose of 20 mg/kg for this agent. With regard to muscle relaxants, in its original report the Task Force advised giving three times the normal therapeutic dosage, i.e., 45 mg alcuronium dichloride or 18 mg pancuronium dibromide. However, the survey reveals that this dosage recommendation is rarely followed in practice, because it does not conform to the ampul strengths available. The Task Force therefore decided henceforth to recommend 50 mg alcuronium dichloride and 20 mg pancuronium dibromide for intravenous administration and 100 mg and 40 mg, respectively, for intramuscular administration. Ampuls of alcuronium dichloride subsequently were taken off the market, so that pancuronium was the only alternative left. In principle, however, another non-depolarizing neuromuscular muscle relaxant can be given intravenously in triple dosage, such as 20 mg vecuronium bromide (Norcuron) (see Table 5). There is as yet no experience with intramuscular administration of vecuronium in humans, but there are no theoretical arguments opposing this.

Table 5. Available non-depolarizing neuromuscular muscle relaxants and their euthanasic intravenous dosage

Muscle relaxant	Starting dose (mg/kg)	Triple dose (mg/70 kg)	Most suitable form	Final recommendation	Remarks
Atracurium	0.3-0.6	94.5	50 mg/5 ml	100 mg (2 amp)	Normal starting dose acts in 15-35

min.
(Tracrium) (5 amp) Duration independent of hepatic metabolism or renal excretion. *Cave* cutaneous reactions as result of histamine release (Adv Drug React Toxicol Ref. 1994;13;23-41).

Gallamine 1 - 2 315 40 mg/2 ml 320 mg (8 amp) Normal starting dose acts in 30-50 min. No
(Flaxedil) (5 amp) longer frequently used in anesthesia.

Mivacurium 0.15 31.5 10 mg/5 ml 30 mg (3 amp) Normal starting dose acts in 15 min.
(Mivacron) (5 amp)

Pancuronium 0.08-0.10 18.9 4 mg/2 ml 20 mg (5 amp) Normal starting dose acts in up to 70 min.
(Pavulon) (50 amp)

Pipecuronium 0.08-0.10 18.9 4 mg/2 ml 20 mg (5 amp) Normal starting dose acts in 30-90 min.
(Arpilon) (12 amp) Is mainly excreted unaltered.

Rocuronium 0.6 126 50 mg/5 ml 150 mg (3 amp) Normal starting dose acts in 30-40 min.
(Esmeron) (12 amp)

Vecuronium 0.08-0.10 18.9 10 mg/5 ml 20 mg (2 amp) Normal starting dose acts in 20-30 min.
(Norcuron) (20 amp) A higher dose may be necessary in hepatic insufficiency.

Rectal euthanasia

In its original recommendations, the Task Force indicated that euthanasia by means of rectal administration of a barbiturate is given no preference. A clyster, in view of the position that the patient must assume (and maintain) for it, is unacceptable while, in the case of suppositories, their availability is greatly dependent upon the patient's ability to retain them. Suppositories may act as laxatives and also carry the risk that the active substance is only slowly released. In addition, the lethal quantity of barbiturate cannot be incorporated into one suppository, so that several suppositories are required. When these are administered at one time absorption is unpredictable, and the large quantity of substance makes severe irritation possible. Repeated administration has the psychological drawback that insertion must be effected in a patient who has already become comatose. In line with the Task Force's views, only a limited number of cases using suppositories were reported. In two cases, it seemed possible to perform euthanasia by administering three suppositories, each containing 1 g barbiturate, every hour. Another case, however, was still ended with a muscle relaxant after 5 hours, after 7 suppositories, each containing 1.2 g barbiturate, had been administered in 30 minutes. All in all, the information obtained gives insufficient reason to alter the viewpoint held by the Task Force in the matter of rectal euthanasia.

4. New Recommendations

Based on the information and considerations in Chapter 3, the KNMP's Euthanasics Task Force has amended its original recommendations as follows:

Parenteral administration

Intravenous administration is the most reliable and rapid way to accomplish euthanasia and therefore can be safely recommended.

A coma is first induced by intravenous administration of 20 mg/kg *thiopental sodium* (Nesdonal) in a small volume (10 ml physiological saline). Then a triple intravenous dose of a non-depolarizing neuromuscular muscle relaxant is given, such as 20 mg *pancuronium dibromide* (Pavulon) or 20 mg *vecuronium bromide* (Norcuron). The muscle relaxant

should preferably be given intravenously, in order to ensure optimal availability. Only for *pancuronium dibromide* (Pavulon) are there substantial indications that the agent may also be given intramuscularly in a dosage of 40 mg. There is as yet no experience with the intramuscular administration of a substance like vecuronium in humans, but there are no theoretical arguments opposing this.

Oral administration

In order to reduce the possibility of vomiting the euthanasic agent, if possible an antiemetic such as metoclopramide should first be given for a day. Actual euthanasia can best take place by administration of a 100-ml potion containing 9 g *pentobarbital sodium* or *secobarbital sodium* . Since this will not always lead to a rapid death, the physician must be prepared, if necessary, to inject a muscle relaxant as well, when death is delayed (e.g., takes longer than 5 hours).

Rectal administration

Euthanasia by the rectal route has such disadvantages that this method may at most be considered when other modes of administration appear to be unfeasible. When this is the case, a suppository containing 1 g *pentobarbital sodium* or *secobarbital sodium* in a fatty base may be considered, the possible dosage being three suppositories every hour. Here it is of great importance to check that the patient's body temperature is not or does not go so low that the suppositories fail to melt thoroughly. As in oral euthanasia, the physician must still be prepared, if necessary, to terminate with a parenteral muscle relaxant when death has not taken place after 5 hours.

5. Dispensing Directions

For oral or rectal euthanasia, it is better not to use existing commercial packs of barbiturates. When barbiturates are to be administered in tablet form, a large quantity of these is likely to be required, with the risk of the patient becoming unconscious before the entire dose has been ingested. The barbiturate, as a sodium salt, is preferably incorporated in a potion or possibly in suppositories. Some specific compounding directions, which replace the original directions from 1987, follow below. In these prescriptions, *secobarbital sodium* may be used instead of *pentobarbital sodium* .

Mixtura nontherapeutica pentobarbitali

Prescription: Pentobarbitalum natricum 9 g
Alcohol 96% v/v 16.2 g (20 ml)
Aqua purificata 15 g
Propylenglycolum 10.4 g (10 ml)
Saccharinum natricum 250 mg
Sirupus simplex 65 g
Anisi aetheroleum 1 gt

Compounding: Dissolve the pentobarbital sodium, while shaking, in the mixture of purified water, propylene glycol and alcohol. Dissolve the saccharin sodium in this also. Add the sugar syrup and anise oil and mix.

Stability: Last date for use, 1 month after compounding date.

Comments: At this concentration pentobarbital sodium does not dissolve completely in water; crystallization of pentobarbital occurs. This appears to be preventable by the addition of propylene glycol and alcohol in the quantities indicated. Then these act as preservatives at the same time. When kept at room temperature, the preparation remains nearly clear for two months. After that, crystallization may occur.

The literature states that a 10% solution slowly decomposes. HPLC studies have revealed that, as concerns chemical stability, this preparation can kept at room temperature for at least 1 month.

Pentobarbital sodium is described in the literature as a substance with a faintly bitter taste. The concentration in this preparation results in not only a bitter taste but, due to its high pH, also a fishlike taste. Therefore a sweetener is added to correct the taste and anise oil is added to mask the alkalinity.

Suppositoria nontherapeutica pentobarbitali
Prescription: Pentobarbitalum natricum 1 g
Adeps solidus (*) q.s.
(*) e.g., Witepsol H15
Compounding: Pentobarbital sodium displaces about 800 mg of the suppository base.
Rub the pentobarbital sodium, reduced to fine powder with aspiration of substance, with a like quantity by weight of the base, heated to 40 C, until a completely uniform compound has been obtained. Add the rest of the base, heated to 40 C.
After the compound has cooled to 34 to 35 C with constant stirring, pour it into 2.7-ml molds.
Stability: Last date of use when kept at room temperature, two weeks after compounding date; when kept in the refrigerator, one month after compounding date.
Comments: Pentobarbital sodium is described in the literature as a hygroscopic substance. This and its alkaline reaction make interaction with the suppository base possible during storage. To see if this affects the speed of release, the melting time was determined. When kept at room temperature for longer than two weeks, the melting behavior appears to change, while after being kept in the refrigerator for one month, it does not change.

6. Supply
6.1 Viewpoint of Chief Inspector's Office
In the legal reporting procedure concerning euthanasia and assisted suicide which the physician must follow as of June 1, 1994, the pharmacist's responsibility receives no attention [Med Contact 1994;49:697-9]. The Public Affairs Ministry, in consultation with the Office of the Superintendent of Public Health, has emphasized that, generally speaking, if a physician is prosecuted for performing euthanasia, this will not lead to the pharmacist's also being prosecuted for complicity.
The Chief Public Health Inspector's Office for Medicinal Drugs likewise takes the view that, in the normal case, the pharmacist may be assumed to be completely exonerated if consultation with the prescribing physician has taken place before supply is made. This of course does not affect the fact that the pharmacist has a special professional responsibility which can be policed by disciplinary means. If the physician does not wish to consult with the pharmacist, he can be required to do so on the basis of Article 29 of the Practice of Pharmaceutics Order:
If the pharmacist or the medical practitioner running a pharmacy suspects an error in a prescription presented to him, or if the prescription is incomplete, illegible or mutilated, he shall immediately notify the person who wrote the prescription. He shall not proceed to make supply until he has obtained the necessary assurance about what has been prescribed.
The Chief Inspector's Office does not consider it necessary for the pharmacist to ascertain ahead of time, in any way, that the physician has acted in accordance with the reporting procedure. Nor is it necessary that he keep a separate record of the euthanasic agents supplied.

6.2. Criteria for Diligence by Professionals
The KNMP's Board of Directors advises pharmacists to keep in mind the following criteria for diligence when supplying euthanasic agents:
- Decision to supply
The decision to supply a euthanasic agent can only be made after timely consultation has taken place between the physician(s) concerned and the pharmacist. At that time the physician must fully inform the pharmacist of the background relevant to the pharmacist. This may be done orally. If necessary, the pharmacist may consult a colleague concerning pharmaceutical aspects, without violating confidentiality vis-à-vis physician and patient.
Pharmacists have the right to refuse to supply euthanasic agents for reasons of principle. If a pharmacist refuses any form of cooperation with euthanasia on the basis of principle, consideration should certainly be given to making the physicians in the vicinity aware of this

in advance.
Pharmacists' assistants should not be involved in the supply of euthanasic agents.
- *Request for supply*
The request for supply of a euthanasic agent should be made in writing. The request must be clear and meet the same requirements that apply to an Opium Act article.
Such a request should be filed away and kept by the pharmacist in the same way as if it concerned an Opium Act article.
- *Supply*
Supply of a euthanasic agent should be made directly by the pharmacist to the physician. The packaging must be furnished with a label that meets the same requirements as demanded for the supply of a medicinal drug. The label should indicate that the packaging and any unused remainder are to be returned to the pharmacist by the physician.
In exceptional cases a request for supply of a euthanasic agent may be made by *number* , instead of by a patient's name. A very clear necessity for this must be present. Traceability of the supply may not be jeopardized by this nor may the possibility of misuse be produced due to this.

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