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Morphine vs. ABT-594: A Reexamination by the Principle of Double Effect

by

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Not long ago, at the request of the nursing staff at a local Catholic hospital, I was consulted as a bioethicist regarding the case of an 86-year-old woman who had metastatic colon cancer and Alzheimer's disease. The non-competent patient was in the last stages of terminal cancer and her attending physician, with the consent of her surrogate decision-maker, decided that all aggressive medical treatment should be terminated and palliative care should be initiated. The only request by the family was that their mother be free of pain. Unsure of the extent of the patient's pain due to the Alzheimer's disease the physician started a morphine drip. The purpose of the morphine was to manage the patient's pain, but everyone knew that the continuous injection of morphine into the patient's vein would gradually kill the patient by depressing her respiration. The nursing staff was very uncomfortable with this because they questioned whether the physician and family were directly trying to shorten the patient's life. The patient did not appear to be in serious pain and without the morphine she would probably live for days or even weeks. Two ethical questions arose: first, was the morphine necessary in this case; and second, was the morphine being used for pain management or was it being used as a form of assisted suicide?

It is estimated that 30 to 40 million Americans depend on morphine, despite its side effects, to relieve severe pain. The use of morphine as a pain reliever, even at high doses, has been accepted by the Roman Catholic Church for centuries under the principle of double effect. The Church argues that there is a moral difference between the effects of actions which

are intended versus those which are foreseen but unintended. "Medicines capable of alleviating or suppressing pain may be given to a dying patient, even if this therapy may indirectly shorten the person's life so long as the intent is not to hasten death."¹ Even though a foreseen but unintended side effect of morphine may be respiratory depression and thus a shortened life span, morphine may be prescribed if the intention is to directly alleviate pain. The problem is that there are critics who believe that the use of morphine for terminal patients is "society's wink to euthanasia."² As long as the "stated" intention is to relieve pain, the use of morphine is legal and ethical. Critics contend that some physicians have used and continue to use morphine as a form of active euthanasia and justify it ethically under the principle of double effect. This has made many inside and outside the medical profession suspicious of morphine's use when administered to terminal patients.

On January 1, 1998 Abbott Laboratories in Chicago announced the development of a new painkiller called ABT-594. According to Michael Williams, a scientist and vice-president at Abbott, "ABT-594 appears to be many times more powerful than morphine, but lacks the serious side-effects...Tests with laboratory animals showed that ABT-594 did not diminish respiration nor cause constipation. Laboratory animals showed no sign of addiction to ABT-594 and the drug appeared to be effective no matter how long it was used."³ At this writing, safety trials with humans are underway in Europe and similar trials will hopefully be undertaken in the United States. The ethical question which arises is: if ABT-594 does prove effective and does not have the side effects of morphine, should the Catholic Church reexamine its position on morphine as a form of pain management considering the objections critics have raised concerning the possible misuse of morphine as a form of active euthanasia?

The purpose of this article is threefold: first, to examine the function of the principle of double effect; second, to compare and contrast morphine and ABT-594 as pain medications; third, to give an ethical analysis of the current controversy on the use of morphine and to determine if it is morally justifiable under the principle of double effect if ABT-594 is approved as a painkiller for humans?

The Function of the Principle of Double effect

The principle of double effect is a fundamental principle in Roman Catholic moral theology, which is complex in its application to practical cases. As the name implies, it refers to one action that produces two effects. One effect is intended and is morally good while the other is unintended and is morally evil. It is not an inflexible rule or mathematical formula, but rather an efficient guide to prudent moral judgment in solving

difficult moral dilemmas.⁴ Historically, many ethicists believe that the premises for the principle can be found in the writings of Thomas Aquinas. However, others contend that the principle may have been understood implicitly many centuries before it was actually formulated. Moralist Joseph Mangan contends that the principle was used implicitly to justify moral actions in the Old Testament.⁵ Explicitly, Mangan argues that Thomas Aquinas is the first to enunciate this principle in his famous explanation of the lawful killing of another in self-defense in the *Summa Theologica*, II-II, q. 64, a.7c. Ethicists Tom Beauchamp and James Childress agree with Mangan on this point.⁶ Josef Ghooos, however, believes that an argument can be made otherwise. "Ghooos showed that the moral solutions from the thirteenth through the sixteenth century were of isolated concrete cases. In the sixteenth century, Bartolomeo Median (1528 – 1580) and Gabriel Vazquez (1551 – 1604) began to name the common factors among the paradigm cases. Finally, John of St. Thomas (1589 – 1644) articulated the factors into the conditions of the principle as such."⁷ However, the four conditions of the principle were not finally formulated until the mid-nineteenth century by Jean Pierre Gury.⁸ The principle of double effect specified four conditions which must be fulfilled for an action with both a good and a bad effect to be morally justified.

1. The action, considered by itself and independently of its effects, must not be morally evil. The object of the action must be good or indifferent.
2. The evil effect must not be the means of producing the good effect.
3. The evil effect is sincerely not intended, but merely tolerated.
4. There must be a proportionate reason for performing the action, in spite of its evil consequence.⁹

It should be noted that a number of moral theologians known as proportionalists have argued that the first three conditions of the principle of double effect are incidental to the principle, and that in reality it is reducible to the fourth condition of proportionate reason. While this is a legitimate argument, it is not the purpose of this article to reopen the controversy on the validity of the first three conditions. This article will remain within the framework of the four conditions of the principle of double effect, as it exists in fundamental moral theology, and apply these conditions to the use of morphine as an ethical painkiller.¹⁰

The use of narcotics to control pain was sanctioned by Pope Pius XII under the principle of double effect. In answer to a group of doctors who posed the question: "Is the suppression of pain and consciousness by the use of narcotics permitted by religion and morality to the doctor and the patient (even at the approach of death and if one foresees that the use of

narcotics will shorten life)?" The Pope stated: "If no other means exist, and if, in the given circumstances, this does not prevent the carrying out of other religious and moral duties: Yes."¹¹ According to the principle of double effect "in this case, of course, death is in no way intended or sought, even if the risk of it is reasonably taken; the intention is simply to relieve pain effectively, using for this purpose painkillers available to medicine."¹² The Church believes that suffering is part of the human condition and has a special place in God's plan of salvation. However, the Church also believes that effective management of pain and suffering is necessary so that the person can die comfortably and with dignity and respect.

The use of morphine to manage pain effectively is ethically justified because it meets the four conditions of the principle of double effect. The first condition allows for the injection of morphine because the action in and of itself is good, in that it effectively alleviates or manages the pain of the patient. While morphine may endanger the patient's life by suppressing respiration, the injection will not directly terminate the patient's life. The second condition allows for the injection of morphine because the good effect is not caused by means of the evil effect. The patient's pain is alleviated by the morphine, not by the patient's death. The good effect and the evil effect happen simultaneously. The third condition allows for the injection of morphine because even though there is the possibility that the morphine may harm the patient, the intention of the physician is to alleviate or manage the patient's pain. Finally, there is a proportionate reason for allowing for the morphine because the patient's pain is intolerable and there is no hope for a cure.¹³ Even though morphine is morally justified by the principle of double effect, considering the serious side effects and the possibility of abuse, would it still be morally justified if there were a viable alternative?

Morphine vs. ABT-594

Morphine is an opium alkaloid and is the prototype of the opioid analgesics. In the non-tolerant patient with severe pain, it provides analgesia at a dose of about 10 mg IM that does not result in severe alterations in consciousness. Morphine affects both the initial perception of pain and the emotional response to it. Total relief from pain is not always possible to achieve, but morphine can reduce the level of distress and suffering. Traditionally, oral morphine has been considered to be ineffective. It is transformed rapidly in the liver and excreted in the urine. However, with upward titration of the dose, oral morphine can be very effective in managing chronic pain. A slow-release tablet that dispenses morphine over 8 to 12 hours and a concentrated oral solution have been developed in attempts to make oral morphine more acceptable. Morphine

sulfate is the most commonly used water-soluble salt. Very low doses of intraspinal morphine (e.g., 5 to 10 mg epidurally or 0.5 to 1 mg intrathecally) can provide long-lasting (up to 24 hour) pain relief postoperatively and in selected nontolerant cancer patients. To date, morphine is the drug most commonly used to manage pain for cancer patients.¹⁴

Adverse effects of morphine are dose-related. These adverse effects include respiratory depression, decreased cough reflex, nausea, vomiting, constipation, itch, sedation, and confusion. Morphine can also produce miosis and can cause contraction of peripheral smooth muscle, the most important effect of which is decreased propulsive movements in the gastrointestinal tract, causing constipation. Morphine causes the venules (capacitance vessels) to dilate, and hypotension may occur in hypovolemic patients or those who suddenly assume the upright position. The development of tolerance to morphine varies from one physiologic system to another (e.g., tolerance develops slowly to the constipating effect, whereas respiratory depression or nausea typically wanes soon after treatment begins). During chronic therapy, an increase in dosage may become necessary to achieve the same degree of pain relief, since the duration of action shortens and the peak analgesic effect decreases.¹⁵

One major criticism of using morphine as a painkiller is that physicians often do not adequately explain to patients or their appropriate surrogate decision-makers how morphine works and what are its side effects. This is because many physicians are not adequately trained in the art of pain management. Instead of referring the terminal patient to a palliative care team which has expertise in pain management, the physician writes an order for morphine and the family is left to watch their loved one die. Questions about the amount of morphine prescribed, who should determine if the dosage should be increased, and what side effects may be expected, are left unanswered. Families are often unprepared for what they will experience. Instead of becoming sedated, many patients experience the reaction agitation. Families find themselves struggling just to keep the patient in bed. Often, physicians will write an order to increase the morphine dosage at the direction of the surrogate, without considering the fact that the surrogate may not be competent to make such decisions.

Christine Campi, executive director of Medical Mission International, explains the sense of frustration and lack of guidelines many family members feel when confronted with the use of morphine for their loved one. In an editorial that appeared in *The New York Times*, Campi explains how her husband's oncologist had written an order that her husband, who was dying of terminal bone cancer with metastasis to the brain, could be given up to 30 milligrams of morphine at her direction. She was the surrogate decision maker. "At doses of 4 to 6 milligrams, my husband

tossed and turned and his breathing was ragged. I asked for 10 milligrams and he began to choke. I asked the nurse to push the morphine pump to 30 milligrams and my husband died, no longer struggling, within two hours. Did I kill him? I don't know. Did I push the morphine pump to warp speed to relieve his suffering or mine?: I don't know."¹⁶ In many instances patients and families are ill-prepared emotionally and clinically to make these decisions concerning the use of morphine. The result is that either the patient's pain is not managed adequately, or the families are left with feelings of guilt that they may have caused the death of the patient. Family members may carry these feelings of guilt and frustration with them for a lifetime. Ethically, similar situations have led many health care professionals and non-health care professionals to question the use of morphine as an effective way to manage pain in terminal patients.

News that Abbott Laboratories had developed a new pain medication that has the benefits of morphine, but none of its side effects, was hailed as a possible major breakthrough in pain management. Apparently ABT-594 acts not through opioid receptors but through a receptor for the neurotransmitter acetylcholine and blocks both acute and chronic pain in rats. ABT-594 was developed from a compound called epibatidine, which was extracted from the skin of an Ecuadorian frog called *Epipedobates tricolor*, at the National Institutes of Health (NIH). In 1976, John Daly, of the National Institute of Diabetes and Digestive and Kidney Diseases, an NIH agency, found epibatidine to be 200 times more potent than morphine at blocking pain in animals. Daly's research came to an abrupt halt, however, when the lab-grown frogs failed to produce the compound and he could no longer collect the *Epipedobates tricolor* because they were placed on the endangered species list. The sample was stored in a freezer for future research. A decade later, Thomas Spande and Martin Garraffo at the NIH, using a nuclear magnetic resonance spectroscopy, determined the chemical structure of epibatidine and found that it resembled nicotine. They learned that it activates the nicotinic acetylcholine receptor. The problem was that while epibatidine is a potent analgesic, it is far too toxic for human use. It was found to cause seizures and even death in lab animals. The results of their findings and a diagram of the chemical structure of epibatidine was published in the journal *Science*. Researchers at Abbot Laboratories realized that epibatidine resembled a group of drugs aimed at the nicotinic receptor that the company was studying in its search for a treatment for Alzheimer's disease. Out of 500 variants they produced and then screened in animals, researchers decided to focus on ABT-594 because it seemed to work against different types of pain and produced few side effects. It also lacked the elements that made the frog compound toxic.¹⁷

In tests conducted by the Abbott team, "ABT-594, nicotine, and morphine were compared in animal models of acute thermal (rat hot box) and persistent chemical (formalin test) pain. In the hot box assay, morphine and nicotine are effective in attenuating the response to pain. ABT-594 was, however, 30 to 70 times more potent in eliciting a dose-dependent antinociceptive effect, with an efficacy similar to that seen with morphine."¹⁸ Researchers also found that in addition to not causing constipation, ABT-594 depresses the respiratory system far less than morphine and makes animals more alert instead of sedating them. In at least one test, animals showed no sign of addiction and ABT-594 appeared to be effective no matter how long it was used. Rats that were taken off ABT-594 after being treated with a high dose for ten days did not suffer the withdrawal symptom of appetite suppression seen after treating with other opioids."¹⁹ These results appear to be very promising, but until human testing is completed both in Europe and in the United States those suffering from severe pain will have to continue to rely on morphine.²⁰

Ethical Analysis

In the event that ABT-594 does prove to be an effective painkiller in humans with minimal side effects, a reexamination of the ethical justification for the use of morphine as a pain reliever for terminal patients, by the principle of double effect, will be necessary. I would argue that morphine would not be ethically justifiable because the fourth condition of the principle of double effect would be violated. The fourth condition states that there must be proportionate reason for performing an action, in spite of its evil consequence. Since morphine can bring on respiratory depression and an earlier death, and ABT-594 does not depress respiration, there is not a proportionate reason for allowing the use of morphine as a pain reliever for terminal patients.

Proportionate reason refers to both a specific value and its relations to all the elements (including premoral evils) in the action.²¹ The Catholic Church allows for the use of morphine today because the value of relieving pain outweighs the premoral evil of the possibility of death from respiratory depression. The question that arises, should ABT-594 prove to be effective, is whether a proportionate reason exists for the use of morphine? To determine this one must examine the criteria for proportionate reason. Ethicist Richard McCormick, S.J., proposes three criteria for determining if a proper relation exists between a specific value and the other elements of an act:

- 1) The means used will not cause more harm than necessary to achieve the value.

2) No less harmful way exists at present to protect the value.

3) The means used to achieve the value will not undermine it.²²

According to McCormick's criteria, if ABT-594 becomes a viable painkiller for terminal patients, the use of morphine would be unethical by all three criteria. First, since morphine does depress respiration and can cause an early death, morphine would cause more harm than necessary. Second, if ABT-594 proves to be effective, then a less harmful way exists to relieve pain for the terminal patient and it will not hasten death. Third, using morphine will undermine the value of human life because it can depress respiration and hasten death. If proven effective, ABT-594 will relieve the patient's pain with no life-threatening side effects. Therefore, in the event that ABT-594 proves effective, the use of morphine as a pain reliever for terminal patients should no longer be morally justified by the principle of double effect.

Conclusion

In our present culture, the debate concerning death and dying is becoming fixated on the patient's right to die with dignity and respect. Patients believe they have the right to determine when and how they should die, and it is the physician's role to assist them. Death with dignity has become synonymous with physician-assisted suicide. As a result, health care professionals are becoming suspicious of one another when certain patients die sooner rather than later. Part of this suspicion lately has focused on the use of morphine as the cause of death. Death by sedation can no longer be ignored. I believe that morphine has been used both as a form of active euthanasia and physician-assisted suicide for years under the ethical guise of the principle of double effect. The morphine drip is used at the discretion of physicians and its use is often arbitrary and inequitable. Oftentimes the decision to use morphine is not made for the good of the patient but for the convenience of the family, the physician and the hospital. In addition, since surrogate decision-makers are often not emotionally and clinically competent to decide whether morphine should be administered and how much should be administered, when death comes, so too, come the agonizing questions. Did I help to kill my father? Was my intention to ease my mother's pain or to ease my own suffering?

Presently, morphine is the most effective drug we have to ease intolerable pain for most terminal cancer patients. If the physician's

intention in using morphine is to manage a patient's pain and the physician is aware of the foreseen but unintended consequence of respiratory depression and a possible early death, then morphine can continue to be justified by the principle of double effect. However, if ABT-594 does prove to be an effective painkiller for terminal patients and it does not have the side effects of morphine, then morphine can no longer be justified under the principle of double effect because it violates proportionate reason. Until the clinical trials with humans prove successful, health care professionals should continue to monitor the use of morphine with terminal patients. The nurses who initiated the ethics consultation on the 8-year-old woman with metastatic colon cancer had legitimate questions concerning the physician's use of morphine. As a result, I called a meeting of the physician, the family, and the nursing staff, so that each had an opportunity to voice his or her concerns. At the end of the hour-long meeting all parties were in agreement that the use of morphine was justifiable and the best course of pain management for this patient. It was a good learning experience for all parties concerned and it emphasized the importance of communication and team work. As medicine becomes more sophisticated and technological, there is a need for physicians, nurses and patients to be in dialogue with one another. Questions need to be asked, alternatives should be suggested, and the hermeneutic of suspicion ought to be employed in order to ensure that all patients are treated with dignity and respect. Only then will suspicion be replaced with trust.

References

1. National Conference of Catholic Bishops, *Ethical and Religious Directives for Catholic Health Care Services*, No. 61 (Washington, DC: United States Catholic Conference, 1995): 23.
2. Thomas Preston, "Killing Pain, Ending Life," *The New York Times*, 1 November 1994, A-15. Preston, a cardiologist and professor of medicine at the University of Washington clarifies his position by stating: "the morphine drip differs from the popular conception of euthanasia in two ways. The first is time. If a physician injects a patient with a highly lethal drug (or a sudden large dose of a drug like morphine), death ensues within seconds and any observer brands the act as euthanasia. A morphine drip takes time, and hospital staff and family come and go during the process. Death is gradual and appears to be of natural causes, and the doctor's absence at the time of death dispels any association between physician and dying. The second difference is stated intent. Physicians, wanting to ease their patient's suffering and not wanting to be identified as the agents of

death, act within the boundaries of normal medical practice. But any form of suffering can be interpreted as pain, and assessment of severity is a matter of professional judgment. If I administer morphine to a suffering and dying patient to relieve pain, I am legal and ethical; if I say it is to end her life, I am illegal and unethical." Ibid.

3. "Poison from Frog Skin Leads to a Painkiller," *The New York Times*, 2 January 1998, A-11.

4. Joseph T. Mangan, S.J., "An Historical Analysis of the Principle of Double Effect," *Theological Studies*, 10 (March, 1949): 41.

5. Ibid. Mangan uses the story of Eleazar in the sixth chapter of the First Book of Machabees to prove this point. "When the Jews were at war with a hostile king, one of the Jews, Eleazar, the son of Saura, performed a very brave deed. He noticed that one of the elephants in the ranks of the enemy was harnessed with the king's harness. Moreover, this elephant was taller than the others and it seemed to Eleazar that the king was on it. Therefore, Eleazar decided to risk the danger of fighting alone through the ranks around the king in order to destroy him. Fighting furiously against the enemy and killing them right and left, he finally reached the elephant. His only hope of bringing down the beast lay on his going between the massive legs and cutting through the tough hide with deadly sword thrusts. This he did, foreseeing that the elephant's fall would kill him too. This brave deed is one of the scriptural deeds justifiable under the principle of double effect." Ibid., 42.

6. Ibid., 43; see also Tom Beauchamp and James F. Childress, *Principles of Biomedical Ethics* 3rd edition (New York: Oxford University Press, 1989), 185, note 15.

7. James F. Keenan, S.J., "The Function of the Principle of Double Effect," *Theological Studies*, 54 (1993): 299; see also Josef Ghooes, "L'Acte à double effet: Etude de théologie positive," *Ephemerides Theologicae Lovanienses* 27 (1951): 30-52.

8. The four conditions of the principle of double effect formulated by Gury state: "1) The ultimate end of the author must be good, that is, the author may not intend the evil effect...2) The cause itself of the effects must be good or at least indifferent, that is, as an act the cause must not be opposed to any law...3) The evil effect must not be the means to the good effect...4) There must be a proportionately serious reason for actuating the cause, so that the author of the action would not be obliged by any virtue to omit the action." See J.P. Gury, *Compendium Theologiae Moralis*, "De actibus humanis," c. 2, 9 (New York: Benzinger, 1874). For further analysis on the historical development of the principle of double effect, see Christopher Kaczor, "Double-Effect Reasoning From Jean Pierre Gury to Peter Knauer," *Theological Studies*, 59 (1998): 297-316; Thomas Cavanagh, "Aquinas' Account of Double effect," *Thomist* 61

(1997): 107-121; Mangan 59-60; and Richard M. Gula, *Reason Informed by Faith: Foundations of Catholic Morality* (New York: Paulist Press, 1989), 270.

9. Gerald Kelly, S.J., *Medico-Moral Problems*, (St. Louis, MO: The Catholic Hospital Association of the United States and Canada, 1958), 13-14.

10. For a more detailed description of the proportionalist's argument, see Keenan, 301-302; Peter Knauer, "La détermination du bien et du mal moral par le principe de double effet," *Nouvelle Revue Théologique* 87 (1965): 356-76; Haig Katchadourian, "Is the Principle of Double Effect Morally Acceptable?" *International Philosophical Quarterly* 27 (1988): 21-30; L. Cornerotte, *Loi morale, valeurs humaines et situations de conflit*, *Nouvelle Revue Théologique* 100 (1978): 502-532; Bernard Hoose, *Proportionalism: The American Debate and Its European Roots* (Washington, DC: Georgetown University Press, 1987); Bruno Schüller, "The Double Effect in Catholic Thought: A Reevaluation," in *Doing Evil to Achieve Good*, eds. Richard McCormick and Paul Ramsey (Chicago, IL: Loyola University Press, 1978), 165-191; and Richard McCormick, S.J., *Notes on Moral Theology: 1965 Through 1980* (Washington, DC: University Press of America, 1981), 751-756.

11. Pius XII, "Address to Delegates to the Ninth National Congress of the Italian Society of the Science of Anesthetics," *Acta Apostolicae Sedis* 49 (February 24, 1957), 147.

12. Congregation for the Doctrine of the Faith, "Declaration on Euthanasia," (Washington, DC: United States Catholic Conference, 1980): 3.

13. Keenan, 305-306

14. Robert Berkow, M.D., ed., *The Merck Manual of Diagnosis and Therapy*, 16th ed. (Rahway, NJ: Merck Research Laboratories, 1992), 1409-1410.

15. *Ibid.*, 1410.

16. Christine Walker Campi, "When Dying is as Hard as Birth," *The New York Times*, 5 January 1998, A-19.

17. Evelyn Strauss, "New Nonopioid Painkiller Shows Promise in Animal Tests," *Science* 279 (January 2, 1998): 32.

18. A.W. Bannon, M.W. Decker, et al., "Broad-Spectrum, Non-Opioid Analgesic Activity by Selective Modulation of Neuronal Nicotinic Acetylcholine Receptors," *Science* 279 (January 2, 1998): 78.

19. Strauss, 33.

20. At this writing, Abbott Laboratories believes that early indications of ABT-594's effectiveness ought to come when the first results from the European safety trials become available. For more details, see Strauss, 33.

21. James J. Walter, "Proportionate Reason and Its Three Levels of Inquiry: Structuring the Ongoing Debate," *Louvain Studies* 10 (Spring, 1984): 32.

22. McCormick's criteria for proportionate reason first appeared in Richard McCormick, *Ambiguity in Moral Choice* (Milwaukee, WI: Marquette University Press, 1973). He later reworked the criteria in response to criticism of this criteria. His revised criteria can be found in *Doing Evil to Achieve Good*, 751-756.