

In Medicine, Timing Matters

Matthew Edlund
Contributing Columnist

Sometimes the new is old. Recent reports have heralded a new "breakthrough" in cancer treatment. Sanjay Gupta of CNN described a study where advanced ovarian cancer was successfully treated by body clock principles. Patients were given chemotherapy timed to the "clocks inside their body," and experienced lesser side effects and longer lives.

The reason such chemotherapy works is that cancer cells and normal cells have pulsatile life cycles. Like most biological processes, cellular reproduction is highly timed. It does not occur equally around the clock. Many chemotherapies work by killing cells when they are most vulnerable, at the time they are splitting and reproducing.

In cancer treatment you want to kill cancer cells and spare normal cells. One way to do that is to find out the time of maximum reproduction. If the normal cells replicate at different hours than cancer cells, you possess a tremendous advantage. You can time chemotherapy to hit the tumor cells as they are growing, sparing as many of the normal cells as you can.

Sometimes you can do this by averaging out the times of cell reproduction for a group of patients. Other times you need to grow up in the lab both tumor and normal cells from individual patients, trying to find the best time is to kill cancer cells. The principle is always the same: destroy your enemy when it is most vulnerable. That's why our military trains its troops

to attack in the early morning hours, when opposing soldiers are asleep or sleepy, at their worst time of day for alertness, strength, and executive decision making. Time cancer chemotherapy correctly and you destroy the tumor while minimizing side effects.

Interestingly, the American news reports did not mention that the French have been giving similar circadian chemotherapy for metastatic colon cancer and other tumors with excellent results since 1992.

Why does it take so long for such an obvious therapy to become more widespread?

Logistical difficulties are part of the problem. To do chemotherapy at specific times for multiple infusions, often when patients are asleep, you don't have them coming to the daytime outpatient clinics typically run by hospitals and oncology groups. Circadian infusions are given around the 24-hour clock. Patients must take the infusion solutions and their computerized pumping gear home with them. As it turns out, many of them like the idea of being treated at home.

Expense is another potential problem. But present day computerized gear minimizes such costs. Cost-benefit analyses for circadian treatments can easily be made with conventionally timed pharmaceutical agents like gleevac, which costs

tens of thousands of dollars a year. In general, chemotherapeutics have jumped in price recently.

Staying Alive



Matthew Edlund M.D.

However, probably the greatest barrier to timed, circadian treatments is mental. Most people do not see that their body processes are highly cyclical. They figure that a pill or a treatment at seven a.m. is pretty much the same as seven p.m. Many adults and their doctors have adopted the metaphor of the "human machine". After all, turning on a computer at 4 a.m. or 4 p.m. should not

make a difference. It does with human beings. Many diseases, perhaps most if properly studied, are cyclical. Most drugs have different effects at different times.

Take asthma. Asthma usually kills between 1 and 4 A.M. The solution is to take asthma medication in the late afternoon-early evening, so peak levels of drug occur when most needed.

Or take another example, the common cold. Nothing really works in treating colds, though washing hands and keeping them away from your face can prevent infection. When we get a cold many of us take anti-histamines to ward off sputum and mucus production. Yet histamine production normally peaks between 11 p.m. and 3 a.m. As antihistamines often make people sleepy, taking them at night has multiple useful effects. People can sleep through the aches of a cold. They can knock down histamine creation when it is highest. And they can prevent the dopiness that comes from taking antihistamines during the daytime.

Consider another common problem,

arthritis. Most studies show taking anti-inflammatory medications four to eight hours before pain hits is the most effective time. Anti-inflammatory drugs like ibuprofen (motrin) have appreciable side effects. Like everything else, these side effects also change with time of day. Usually gastric damage caused by anti-inflammatories is worst during the daytime. Ulcer incidence is usually cut by about half when anti-inflammatories are given at night.

If you have arthritis pain when waking, taking ibuprofen at night should maximally decrease your pain and your gastric side effects.

Improvements in treatment effectiveness of 10 to 15% often incite headlines. Merely changing the timing of a drug can change side effects and potential effects two, three, or more fold. Yet these results are virtually never heralded in the press.

Why? The main reason is people don't think about timing. Another reason is that they are uncommonly studied. The whole field of chronopharmacology, the timing of medications, is poorly funded. Drug companies, already reeling from high development costs, don't want to spend more money defining the best times to use their drugs.

Yet some progress is being made. Most people are now told to take statin drugs at night. Cholesterol is normally produced during the night. Using statin drugs at night markedly increases their effectiveness.

We must recognize that most of the illnesses that afflict us are marked by time. They increase and decrease in predictable ways during the day and during seasons. Timing surgery for breast cancer according to the menstrual period affects survival.

It's time to pay attention to timing. The Romans said time rules life. Often timing of treatments determines our survival.

Dr. Matthew Edlund, M.D., M.O.H., director of The Center for Circadian Medicine, is an expert on applied public health, sleep medicine and psychiatry. He graduated from Amherst, S.U.N.Y. Downstate Medical Center and Harvard and now practices at 1241 S. Tamiami Trail. His email: doctoredlund@comcast.net.



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