Background: Rofecoxib (marketed by Merck & Co. under the name Vioxx) is a nonsteroidal anti-inflammatory drug. It gained widespread acceptance in treating patients with arthritis and other conditions causing chronic or acute pain. In 2004, it was withdrawn due to the increased risk of heart attack and stroke associated with its long-term, high-dosage use. More controversially, it was disclosed that Merck had withheld information about rofecoxib’s risks for over five years, resulting in 88,000–140,000 cases of serious heart disease.

The risk mechanism is understood to work primarily as follows: rofecoxib is a COX-2 (cyclooxygenase) inhibitor, while COX-2 regulates prostacyclin, which is a potent vasodilator and inhibitor of platelet aggregation. Thus, long-term use of Vioxx was suppressing two effects that would help keep open the coronary arteries. This decreases blood flow to heart (and other) tissue, which could then become ischemic or die.

1. Research Ethics and Biomedical Engineering Practice. While rofecoxib is no longer on the market, some have argued that its advantages in treating pain outweigh the risks for some patients. On the other hand, once a drug is available on the market, there are few effective controls, as physicians may prescribe it for off-label usages.

Consider a new research project to test rofecoxib on patients with a late-stage chronic inflammatory disease, in which the heart disease risks are considered less important than the potential benefits.

A. (5 marks) Outline three considerations to be incorporated into the information letter and consent form for the participants and their caregivers in this study. Assume that these subjects may be unable to properly consent (ie. due to the chronic condition and possible stroke).

B. (10 marks) In some studies, participants are paid to participate.

Part A: Is this ethical? Select a specific ethical framework from the ones we considered in class, and frame your arguments in terms of the categories of the ethical framework.

Part B: Is there a maximum value of compensation that is ethical? Choose a maximum dollar value for compensation, and briefly justify it ethically.

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1 en.wikipedia.org/wiki/Rofecoxib
2 Vaithianathan et al, Drug Safety, 2009:32:335-343
C. (5 marks) Through court cases, we know that Merck & Co. actively covered up problems with Vioxx. Would it make a difference if the failure to detect problems was due to incompetence, rather than deliberate falsification? Choose whether deliberate errors are a) worse, b) equal to, or c) better than ones due to incompetence. Using an ethical theory, briefly justify your choice.

2. Sampling and statistical methods. Consider the project to test rofecoxib (in Q1): Patients with late-stage chronic disease are recruited. An experimental group (E) receives the drug and a control group (C) receives a standard treatment (ibuprofen). Participants are evaluated on two variables: 1) cardiac health, as measured by left ventricular ejection fraction (LVEF), and 2) pain levels (PAIN), as measured by a survey of patients on a scale of 1–10.

The following table of t-test values for various degrees of freedom (DF) and one-tailed confidence may help:

<table>
<thead>
<tr>
<th>DF</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>50</th>
<th>100</th>
<th>∞</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>2.92</td>
<td>2.35</td>
<td>2.02</td>
<td>1.81</td>
<td>1.72</td>
<td>1.68</td>
<td>1.66</td>
<td>1.65</td>
</tr>
<tr>
<td>99%</td>
<td>6.96</td>
<td>4.54</td>
<td>3.37</td>
<td>2.76</td>
<td>2.53</td>
<td>2.40</td>
<td>2.36</td>
<td>2.33</td>
</tr>
</tbody>
</table>

A. (5 marks) Participants are randomly assigned to groups E and C, and are not told what medication they receive; however, the experimental staff do know the participant group assignment. What type of “blinding” would describe this experiment. Briefly discuss the importance of blinding and the ways it can impact the experimental results.

B. (5 marks) The study plans to measure the fractional decrease in LVEF after one year, as

\[ f = \frac{LVEF_0 - LVEF_1}{LVEF_0} \]

where LVEF_0 is the LVEF at the start of the study, and LVEF_1 is the LVEF at one year. What size of study is required to detect a difference between E and C groups at 99% confidence level?

Assume that we can estimate the means (\( \overline{f} \)) and standard deviations (\( \sigma_f \)) in \( f \) as follows: for E, \( \overline{f} = 0.2, \sigma_f = 0.4 \), and for C, \( \overline{f} = 0.3, \sigma_f = 0.4 \).

C. (5 marks) We want to test whether there is any relationship between the change in heart function, \( f \), and the change in experienced pain. A change in pain perception value, \( p \), is calculated:

\[ p = \frac{PAIN_0 - PAIN_1}{PAIN_0} \]

where PAIN_0 is the survey reported PAIN score at the start of the study, and PAIN_1 is the value at one year. Consider the following measures (a,b,c), and indicate whether they are a valid statistical analysis of LVEF and PAIN. If not, indicate a reason why. (Consider the measurement scales of the two variables.)

a) Testing whether Pearson’s correlation (\( r \)) between \( f \) and \( p \) is larger than a threshold.

b) Testing whether group E’s average \( \overline{p_E} \) is larger than group C’s \( \overline{p_C} \).

c) Testing whether patients with PAIN \( \geq 5 \) have higher \( f \) than those with PAIN < 5.

D. (5 marks) From this study, we could calculate a positive predictive value (PPV), which would indicate the likelihood that a participant using rofecoxib would have a large decrease in LVEF (for example, assume PPV is 20% for a member of group E to experience \( f > 0.2 \)).

How well does this PPV measure the risks of rofecoxib? Consider that the participant group is selected based on having late-stage chronic disease.
3. Cells and electrophysiology

A. (5 marks) In a healthy person, there is no ischemia and the heart functions normally. Sketch the heart and indicate the direction of propagation of electrical signals on its surface. Also, sketch the normal (lead I) ECG signal, and indicate which peak corresponds which phase of electrical signal propagation in the heart.

B. (5 marks) Plaque in a coronary artery reduces blood flow to the heart muscle “downstream” of the artery. This reduced blood flow (called ischemia) slows the propagation of action potentials through the muscle. Sketch the propagation of electrical signals on the surface of the heart where a small region is ischemic. Indicate how this defect in propagation can result in ventricular fibrillation.

C. (5 marks) It is often recommended for a patient to improve their health by regular aerobic exercise. During a long run, as a patient perspires, the blood volume will decrease. What will happen to the resistance to blood flow of small arteries? Is this a greater risk in this patient group than in a healthy person doing the same exercise? To compensate for the perspiration, the patient drinks water (instead of an isotonic energy drink). This water is then absorbed into the blood. Describe the flow of water, via osmosis, between the blood and tissue in this case.

4. Oxygen transport (heart and lungs), and biomechanics

A. (5 marks) Heart muscle is has complex structure, and is inhomogeneous, anisotropic, and has different active and passive properties. Describe what these terms mean for biological materials, in contrast to most engineering materials, such as steel.

B. (5 marks) A key measure of the efficiency of the heart’s activity is the left ventricular ejection fraction (LVEF). If part of the heart muscle dies (infarction), this can lead to an insufficiency of the heart valves. Define LVEF and explain briefly how: a) infarction can lead to valve insufficiency, and b) insufficiency of the aortic valve leads to a decrease in LVEF.

C. (5 marks) Consider a case of aortic valve insufficiency such that the heart has LVEF = 0.5. The heart is beating at 90 beats/min with a cardiac output (CO) = 4.5 L/min. Systolic and diastolic pressure are 150 and 100 mmHg respectively. Sketch a diagram as a function of time of the a) left ventricular pressure, b) aortic pressure, and c) ventricular volume.

D. (5 marks) When the left ventricle is unable to provide enough pressure to adequately drive blood through the body, the right ventricle will often increase its output pressure (P_{RV}), resulting in a condition called congestive heart failure (CHF), which results in high blood pressures in the lung tissue. Sketch a diagram of the pressures in the heart chambers and the systemic and pulmonary arteries and veins (approximate pressure values are fine for this question). Explain how an increase in P_{RV} will a) help increase the left ventricular pressure, and b) cause increased pressure in lung tissue.

E. (5 marks) In the lungs, the blood-gas interface is very thin. This means that any increase in blood pressure in the lungs can lead to fluid being “pushed” into the tissue and air spaces (a condition known as oedema). This fluid will stiffen the lungs and also be pulled downward by gravity and accumulate in the lower regions of the lungs. Explain two mechanisms by which oedema will decrease lung efficiency and increase the work of breathing.

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4webmd.com/fitness-exercise/exercise-healthy-heart