

# International Survey of 160 Anesthetists' Opinions on Clinically Relevant Improvements in Anesthetic Drugs and Their Cost

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## Introduction

A multi-choice questionnaire was developed using SurveyMonkey. It was designed to maintain the respondents' ignorance of what drug was put forward as the alternative to propofol. The questions refer to properties of the "ideal" anesthetic as proposed many years ago by Prof. John Dundee and how a new anesthetic might approach that ideal compared with propofol. In the 160 responses, only five were from those sent the survey by Drawbridge (first order respondents). Those people then forwarded the survey to others they knew (second order respondents) without any reference to Drawbridge, Colin Goodchild, Phaxan™, alphaxalone, Althesin or steroid anesthesia or cyclodextrins or Melbourne/Australia. Those recipients were blinded as to the source of the inquiry and so too were those to whom the second order respondents had passed the survey URL. For each individual the ip address of the computer used was noted; all are different so multiple answers from the same individual did not occur.

## Summary

The summary of the responses for each of the 14 questions asked appears below. The overall conclusions from this survey are:

1. Cardiovascular stability during anesthesia proved to be a very important factor in choice of intravenous anesthetic with 65.6% respondents saying that lower depression of blood pressure would make them very likely and 27.4% respondents somewhat likely to choose the new anesthetic instead of propofol
2. 58.9% of respondents are very likely and 31.6% somewhat likely to use the new anesthetic based on its improved safety profile alone compared with propofol
3. 40.1% of respondents are very likely and 36.9% somewhat likely to use the new anesthetic because of its water solubility alone
4. 21.9% of respondents are very likely and 21.3% somewhat likely to use the new anesthetic if it has the same fast onset and offset compared with propofol
5. when a price of \$10 per dose for the new agent (several times the current price of propofol) is put into the equation, 5.3% of respondents said they would definitely and 11.9% would probably buy the new anesthetic even in a perfectly fit patient
6. when a price of \$10 per dose for the new agent (much higher than the current price of propofol) was put into the equation in question 12, significantly more anesthetists would use the new agent when they had patients with the following common clinical situations:
  - a. an elderly patient with heart disease - 41.1% would buy the new anesthetic definitely and 42.4% would probably buy the new anesthetic
  - b. an elderly patient with early cognitive decline - 31.8% would buy the new anesthetic definitely and 35.1% would probably buy the new anesthetic on the understanding that there was evidence that the new anesthetic could protect such brains where conventional agents do not
  - c. a patient with severe respiratory disease - 26.5% would buy the new anesthetic definitely and 31.1% would probably buy the new anesthetic

- d. a case of multitrauma - 28.5% would buy the new anesthetic definitely and 45.7% would probably buy the new anesthetic on the understanding that the new drug would cause less falls in blood pressure
- e. a case of head injury - 31.1% would buy the new anesthetic definitely and 43.0% would probably buy the new anesthetic on the basis that the new agent is cerebrally protective with better cardiovascular stability than propofol
- f. in questions 9 and 10 it is clear that brain protection can be a very important factor in choosing the new anesthetic compared with propofol; 56.1% - 65.6% respondents saying they would be very likely to use the new anesthetic and an average of 30% respondents saying that they would be somewhat likely to choose to use the new protective anesthetic for that property.

## Data Relevant to Analysing the Survey Results

**1**

How commonly do the sicker patients present for anesthesia and surgery compared with the fitter patients. The ASA classification is useful for this and can be found in many research papers. For example:

***ASA classification and perioperative variables as predictors of postoperative outcome. Wolters U et al. British Journal of Anesthesia 1996; 77: 217-222***

A breakdown of 6000 surgical patients by ASA grade and preoperative conditions are shown in tables below taken from the paper cited above. Patients with ASA grades 3 and above are regarded as significantly increased risk. Those are cases relevant to the survey questions on safety. 40% of all surgical patients appear in the sicker ASA grades and many of these are over 65 years.

*Table 1 American Society of Anesthesiologists' (ASA) physical status classification*

Class	Description
I	Healthy patient
II	Mild systemic disease—no functional limitation
III	Severe systemic disease—definite functional limitation
IV	Severe systemic disease that is a constant threat to life
V	Moribund patient unlikely to survive 24 h with or without operation

*Table 3 ASA classification of all patients*

	<i>n</i>	%
ASA I	1133	18
ASA II	2685	42.6
ASA III	2181	34.6
ASA IV	290	4.6
ASA V	15	0.2

Table 4 Incidence of specific preoperative disease status

	n	%
Anaemia	501	8
Arterial hypertension	1817	28
Previous myocardial infarction	272	4
Previous stroke	460	7
Positive smoking history	1823	28
Severe bronchopulmonary disease	1353	21
Diabetes mellitus	685	11
Acute or chronic renal failure	685	11
Major gastrointestinal disease	1540	24

2

What is the proportion of patients over 65 years who are higher risk ASA grades 3 and 4?

**A 5-year survival study of general surgical patients aged 65 years and over. A. E. EDWARDS, et al Anesthesia, 1996, Volume 51, pages 3-10**

This paper shows that 32% of patients admitted for general surgery over 65 years of age are higher risk ASA grades 3 and 4. It is these patients that the survey respondents would consider for the new anesthetic compared with propofol.

3

Data from the United States for 2009 (National Center for Health Statistics) show that 17.8 million of the 48 million surgical procedures (37%) performed annually in the US are performed in patients over 65 years.

14% of these 17.8 million surgical cases have cognitive decline = 2.492 million - these are the cases highlighted in the survey in question 10 when 95% of respondents said they were highly likely (65%) or somewhat likely (30%) to use the new drug with properties of protecting vulnerable brains from cognitive decline.

4

Very recent evidence, published by **Kline et al in Anesthesiology 2012:116; 603-12** has highlighted the issue of the effect of anesthesia and surgery on the rate of cognitive decline. They showed that surgery and anesthesia in elderly human patients increased cognitive decline in subjects with mild cognitive impairment to the extent that they will reach the point of needing aged care two years earlier than subjects who had not undergone surgery and anesthesia. This acceleration in cognitive decline is caused by inflammatory processes in the brain being activated and increased by surgery and the anesthetic drugs. Drugs in the Drawbridge portfolio, including the intravenous anesthetic Phaxan™ are highly likely to prevent this cognitive decline. This has enormous societal and economic importance. Since the majority of over 65's presenting for surgery will not have been screened for cognitive decline, the argument for using the new anesthetic in all 17.8 million anesthetics in that age group in the US is made as an attempt to impact on the societal cost of US\$20,000,000,000 for aged care in the extra 250,000 cases per year caused by post anesthesia and surgery cognitive disability.

# The Survey

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## What Properties of a New Intravenous Anesthetic Will Make me Use it rather than propofol?

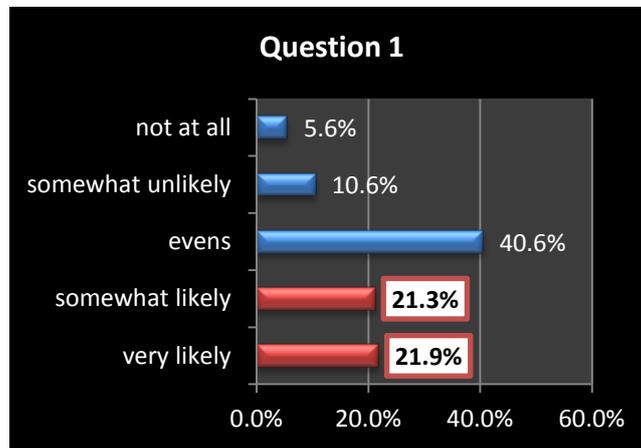
### introduction to survey

Fewer than 10% of consultant anesthetists practising today have known the practice of anesthesia before the introduction of propofol in 1982. Propofol is now used in over 95% of all cases of anesthesia for surgery, procedural sedation and intensive care sedation. It is a well loved drug that is used skilfully and safely. Propofol is sold cheaply as a generic drug. This low price combined with difficulties in manufacturing associated with its lipid formulation has led to significant shortages of supplies particularly in the United States where anesthetists have been forced to use older drugs with much less favorable pharmacodynamic and pharmacokinetic profile. Having said that, propofol itself does have significant issues with its use such as:

- pain on injection in 48% of cases
- the lipid emulsion is prone to get infected by bacteria; it cannot be filtered or sterilised and it cannot be inspected for foreign particles before injection; leading to many instances of contamination and patient infections
- the lipid emulsion is incompatible with plastics and it causes problems with smooth operation of plastic syringes
- the lipid emulsion causes a toxicity reaction in larger doses in the sicker patients in the ICU
- propofol causes hypotension, especially in the patient who has compromised cardiovascular function
- propofol causes respiratory depression
- the previous last two points mean that the ratio of lethal dose to therapeutic dose (the therapeutic ratio) is low for propofol (approx 5). Further, in recent years propofol has been caught up in the controversial discussions surrounding all other modern anesthetics and involving the FDA; the issue of anesthetic drugs causing neuronal damage and long-term cognitive dysfunction in very young and aged patients.

For these reasons over a dozen pharmaceutical companies worldwide are working to develop a new intravenous anesthetic to complement or replace propofol.

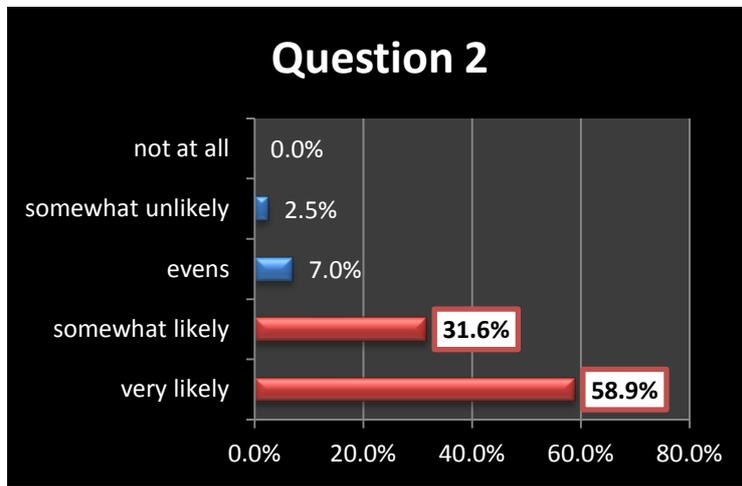
The questions in this survey concern what properties an anesthetic might possess that would lead you to change the intravenous drug you use for anesthesia by bolus injection and infusion. Below are the properties of one of the new anesthetic formulations that have been developed. For each question and property we ask you to rate whether this property would lead you to use the new anesthetic instead of propofol.



**Q1. The new iv anesthetic causes anesthesia with fast onset, and offset timing equal with propofol. How likely is this property going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	21.9%	35
somewhat likely	21.3%	34
evens	40.6%	65
somewhat unlikely	10.6%	17
not at all	5.6%	9
Comment?		18
<i>answered question</i>		<b>160</b>
<i>skipped question</i>		<b>0</b>

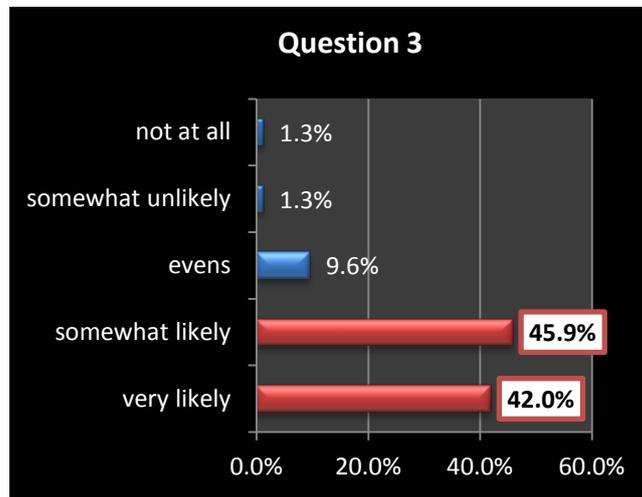
43.2% of 160 respondents are very likely or somewhat likely to choose Phaxan™ instead of propofol if we can show it has onset and offset times equal with propofol



**Q2. The new iv anesthetic is six times safer than propofol; its therapeutic index is greater than 30 compared with 5 for propofol. How likely is this property going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	58.9%	93
somewhat likely	31.6%	50
evens	7.0%	11
somewhat unlikely	2.5%	4
not at all	0.0%	0
Comment?		11
<i>answered question</i>		<b>158</b>
<i>skipped question</i>		<b>2</b>

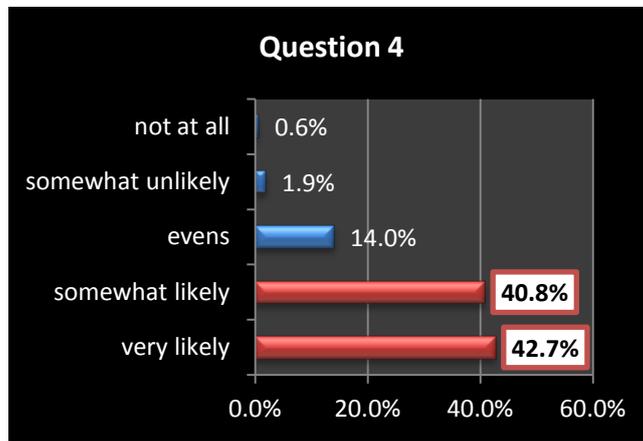
96.5% of 158 respondents are very likely or somewhat likely to use Phaxan™ instead of propofol if we show it to have a much higher therapeutic index than propofol



**Q3. The new iv anesthetic has a pharmacokinetic profile suitable for prolonged infusions slightly better than propofol with more predictable recovery after long infusions. How likely is this property going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	42.0%	66
somewhat likely	45.9%	72
evens	9.6%	15
somewhat unlikely	1.3%	2
not at all	1.3%	2
<i>answered question</i>		<b>157</b>
<i>skipped question</i>		<b>3</b>

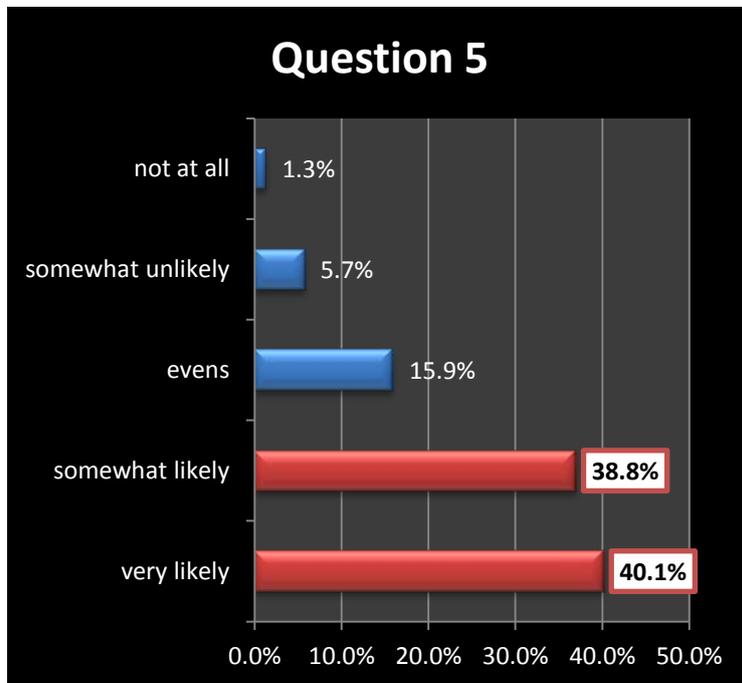
87.9% of 157 respondents are very likely or somewhat likely to use Phaxan™ instead of propofol for prolonged intravenous anesthesia if the pharmacokinetic profile of Phaxan™ showed it to have a more predictable recovery



**Q4. The new iv anesthetic does not accumulate on prolonged exposure and its metabolites are inactive and non-toxic making its metabolic profile equal to or slightly better than propofol. How likely is this property going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	42.7%	67
somewhat likely	40.8%	64
evens	14.0%	22
somewhat unlikely	1.9%	3
not at all	0.6%	1
Any further comment?		7
<i>answered question</i>		<b>157</b>
<i>skipped question</i>		<b>3</b>

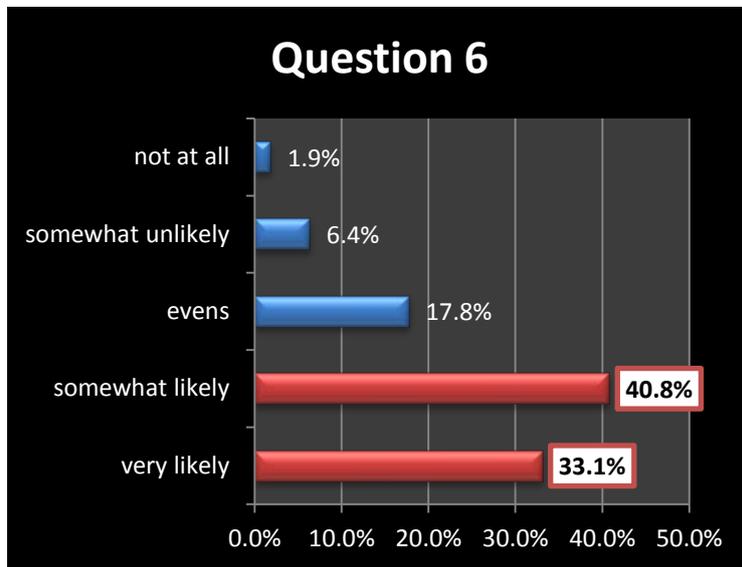
83.5% of 157 respondents were very likely or somewhat likely to use Phaxan™ instead of propofol if Phaxan™ did not accumulate on prolonged exposure and it had non toxic metabolites with a metabolic profile equal to or better than propofol



**Q5. The new iv anesthetic is a clear water-soluble preparation using an FDA approved excipient to achieve water solubility. This is filterable with none of the infection, issues associated with propofol. The solution looks like water and feels like that on injection from a plastic syringe; no stiction. How likely are these properties going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	40.1%	63
somewhat likely	36.9%	58
evens	15.9%	25
somewhat unlikely	5.7%	9
not at all	1.3%	2
Comment?		19
<i>answered question</i>		<b>157</b>
<i>skipped question</i>		<b>3</b>

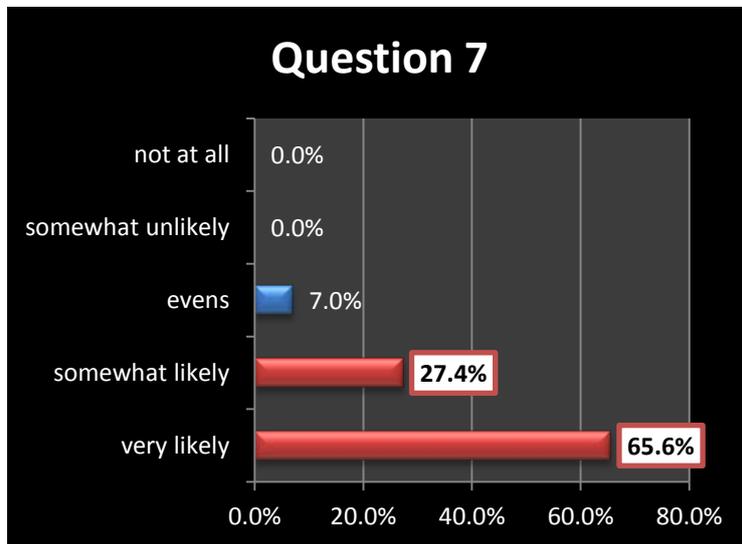
77% of 157 respondents were very likely or somewhat likely to use Phaxan™ instead of propofol because of its water-based formulation



**Q6. The new iv anesthetic's clear water-soluble preparation has no lipid toxicity issues that are sometimes associated with the propofol lipid formulation. How likely is this property going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	33.1%	52
somewhat likely	40.8%	64
evens	17.8%	28
somewhat unlikely	6.4%	10
not at all	1.9%	3
<i>answered question</i>		<b>157</b>
<i>skipped question</i>		<b>3</b>

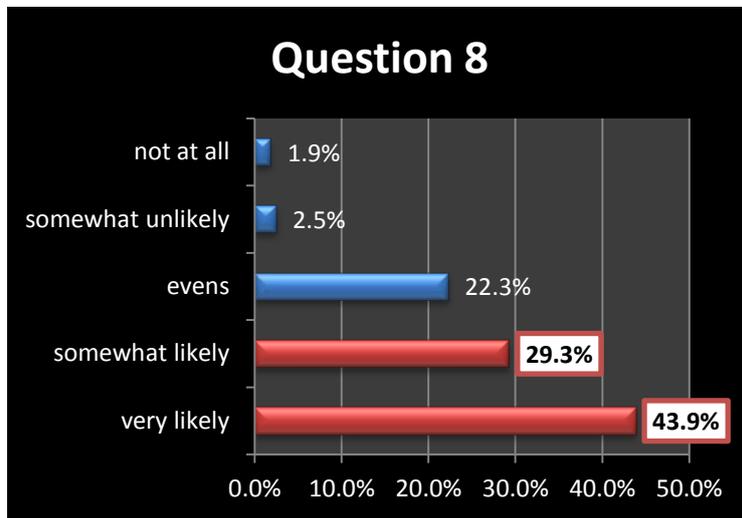
73.9% of 157 respondents were very likely or somewhat likely to use Phaxan™ instead of propofol because the new anesthetic does not involve administration of lipid and exposing the patient to lipid toxicity



**Q7. The new iv anesthetic causes significantly less depression of blood pressure than propofol. How likely is this property going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	65.6%	103
somewhat likely	27.4%	43
evens	7.0%	11
somewhat unlikely	0.0%	0
not at all	0.0%	0
Comment?		8
<i>answered question</i>		<b>157</b>
<i>skipped question</i>		<b>3</b>

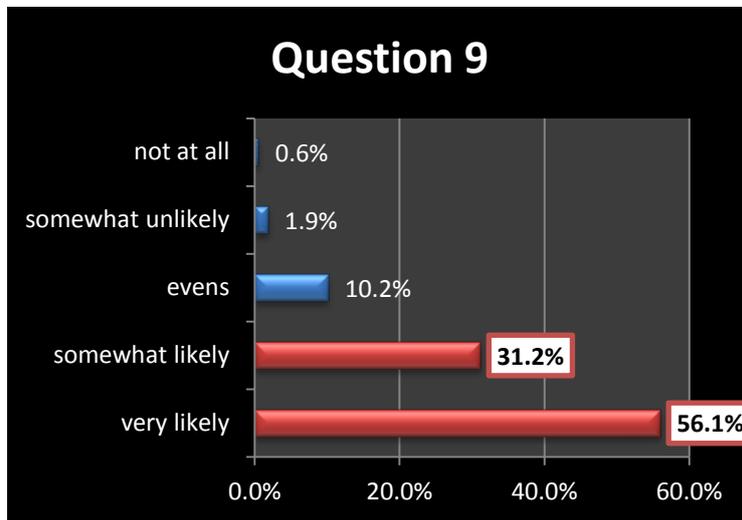
93% of 157 respondents were very likely or somewhat likely to use Phaxan™ instead of propofol because it causes less cardiovascular depression



**Q8. The new iv anesthetic causes significantly less respiratory depression than propofol. How likely is this property going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	43.9%	69
somewhat likely	29.3%	46
evens	22.3%	35
somewhat unlikely	2.5%	4
not at all	1.9%	3
Comment?		9
<i>answered question</i>		<b>157</b>
<i>skipped question</i>		<b>3</b>

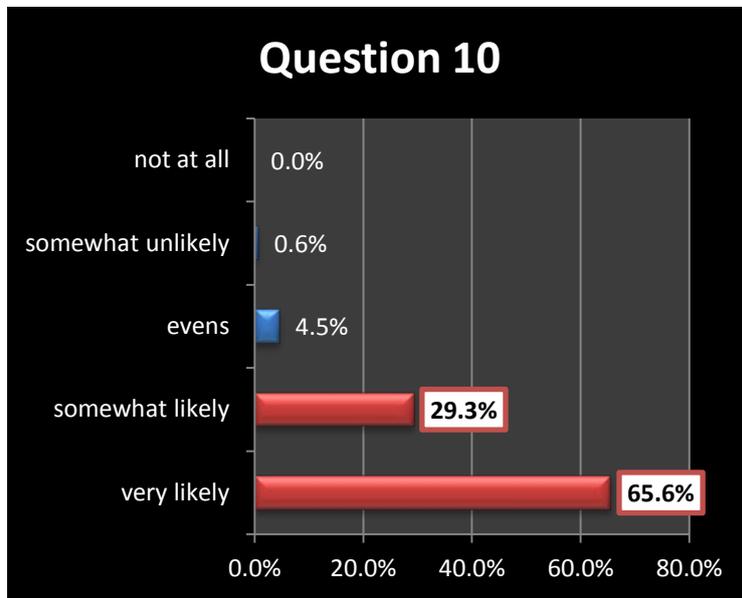
73.2% of 157 respondents were very likely or somewhat likely to use Phaxan™ instead of propofol because it causes less respiratory depression



**Q9. The new iv anesthetic causes neuroprotection at doses that cause significantly less cardiovascular and respiratory depression than propofol. How likely is this property going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	56.1%	88
somewhat likely	31.2%	49
evens	10.2%	16
somewhat unlikely	1.9%	3
not at all	0.6%	1
Comment?		6
<i>answered question</i>		<b>157</b>
<i>skipped question</i>		<b>3</b>

87.3% of 157 respondents were very likely or somewhat likely to use Phaxan™ instead of propofol for neurotrauma [neurosurgery, ICU management of stroke or head injury] where the dose of propofol is well known to cause problematic cardiovascular depression



**Q10. The new anesthetic, protects young and ageing brains from neuronal damage and subsequent cognitive deficit caused by assaults such as surgery, sepsis, pain and trauma, a property not possessed by other modern anesthetic drugs. How likely is this property going to make you change from choosing propofol to using the new iv anesthetic drug in your practice?**

Answer Options	Response Percent	Response Count
very likely	65.6%	103
somewhat likely	29.3%	46
evens	4.5%	7
somewhat unlikely	0.6%	1
not at all	0.0%	0
Comment?		12
<i>answered question</i>		<b>157</b>
<i>skipped question</i>		<b>3</b>

94.9% of 157 respondents were very likely or somewhat likely to use Phaxan™ instead of propofol if we are able to show that Phaxan™ anesthesia causes neuroprotection during the course of surgery or in conditions that cause neural stress [sepsis, pain, trauma].

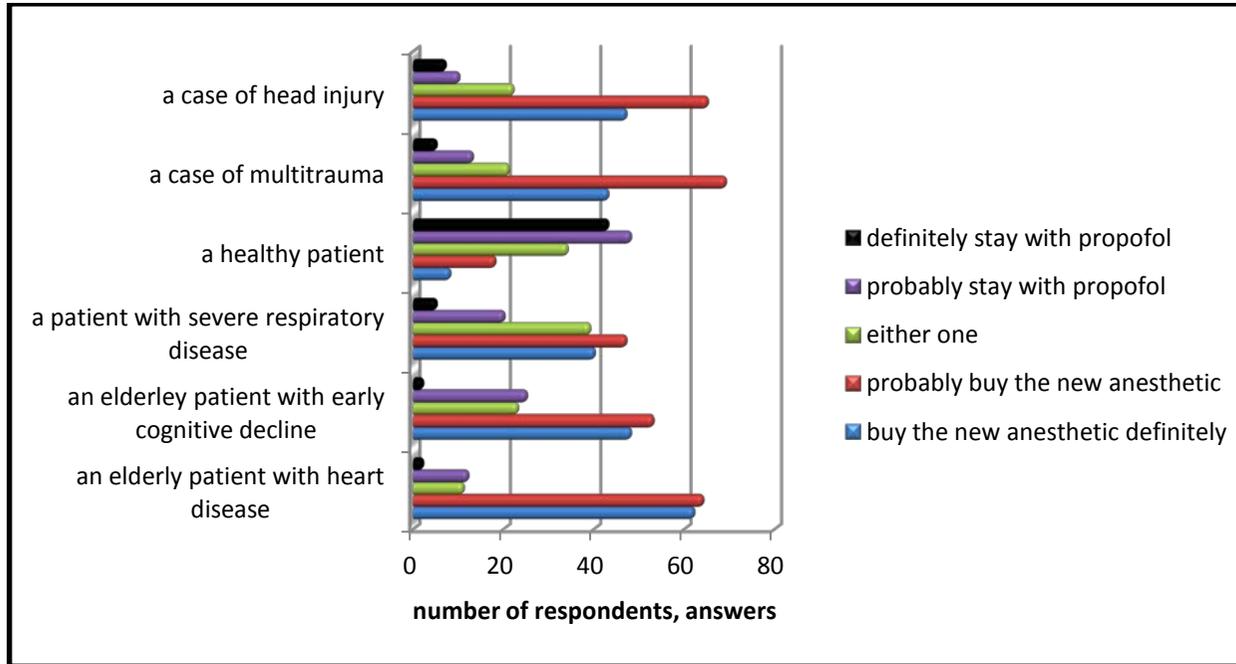
Q11. The new anesthetic has all of the properties described in questions 1-10 above. Given these properties, TAKEN TOGETHER AS A WHOLE, if the new anesthetic were available in your hospital today, please indicate your choice, new anesthetic or propofol for each of these clinical conditions:

Answer Options	use new anesthetic definitely	probably use new anesthetic	either one	probably use propofol	definitely use propofol	Response Count
an elderly patient with heart disease	91	56	6	2	0	155
a patient with severe respiratory disease	55	61	33	6	0	155
a healthy patient	19	28	77	21	10	155
a case of multitrauma	69	71	11	4	0	155
a case of head injury	74	63	14	3	1	155
any other comment?						16
<i>answered question</i>						155
<i>skipped question</i>						5

Q12. Now to one last question; that of costs and pricing. A new drug is always sold at a higher price compared with a generic in its field. The new drug gains marketing approval if safe and effective and finally gets on a hospital list or formulary if the balance of price and improvements in efficacy is favorable. Assuming the new anesthetic has all of the properties described in questions 1-10 above AND given these properties, TAKEN TOGETHER AS A WHOLE, would you encourage your hospital to pay the higher price e.g., \$10 per dose? Please indicate your choice, new anesthetic or propofol for each of these clinical conditions:

Answer Options	buy the new anesthetic definitely	probably buy the new anesthetic	either one	probably stay with propofol	definitely stay with propofol	Response Count
an elderly patient with heart disease	62	64	11	12	2	151
an elderly patient with early cognitive decline	48	53	23	25	2	151
a patient with severe respiratory disease	40	47	39	20	5	151
a healthy patient	8	18	34	48	43	151
a case of multitrauma	43	69	21	13	5	151
a case of head injury	47	65	22	10	7	151
Please fee free to add a comment						18
<i>answered question</i>						151
<i>skipped question</i>						9

Answers to Question 12: if Phaxan™ cost more...



Q13. Please confirm you are a practising anesthetist at junior (in training) grade or senior level		
Answer Options	Response Percent	Response Count
trainee anesthetist	30.7%	46
consultant/senior professional specialist anesthetist	69.3%	104
Comment?		5
<i>answered question</i>		150
<i>skipped question</i>		10

Q14. Please indicate your hospital practice. Mark as many choices as applicable		
Answer Options	Response Percent	Response Count
academic hospital	86.7%	130
private hospital or clinic	26.7%	40
endoscopy clinic	21.3%	32
day case center	34.7%	52
cardiothoracic/vascular anesthetist	18.0%	27
neurosurgical anesthetist	24.0%	36
paediatric/neonatal anesthetist	22.7%	34
intensivist	17.3%	26
orthopedic anesthesia	32.0%	48
anesthetic service for general surgery	48.0%	72
Comment?		8
<i>answered question</i>		150
<i>skipped question</i>		10

Q15. What is your geographical location		
Answer Options	Response Percent	Response Count
North America	8.7%	13
South America	0.0%	0
Western Europe	34.0%	51
Eastern Europe	0.0%	0
Asia	11.3%	17
Australia/New Zealand	46.0%	69
anything else?		7
<i>answered question</i>		150
<i>skipped question</i>		10